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# Nationwide analysis of treatment outcomes in children and adolescents routinely treated for tuberculosis in The Netherlands

Fajri Gafar,[1*] Natasha van't Boveneind-Vrubleuskaya,[2,3*] Onno W. Akkerman,[4,5] Bob Wilffert,[1,2] Jan-Willem C. Alffenaar[2,6,7]

1. University of Groningen, Groningen Research Institute of Pharmacy, Unit of PharmacoTherapy, -Epidemiology, and -Economics, Groningen, The Netherlands.
2. University of Groningen, University Medical Center Groningen, Department of Clinical Pharmacy and Pharmacology, Groningen, The Netherlands.
3. Department of Public Health TB Control, Metropolitan Public Health Services, The Hague, The Netherlands.
4. University of Groningen, University Medical Center Groningen, Department of Pulmonary Diseases and Tuberculosis, Groningen, The Netherlands.
5. University of Groningen, University Medical Center Groningen, Tuberculosis Center Beatrixoord, Haren, The Netherlands.
6. University of Sydney, Faculty of Medicine and Health, School of Pharmacy, Sydney, Australia.
7. Westmead Hospital, Sydney, Australia

*FG and NBV Contributed equally to this manuscript

**Corresponding author:**

Fajri Gafar

University of Groningen,

Groningen Research Institute of Pharmacy,

Unit of PharmacoTherapy, -Epidemiology and -Economics,

Antonius Deusinglaan 1 (room: 3214.0450),

9713 AV Groningen, The Netherlands,

Tel: +31 50 36 32476

E-mail: f.gafar@rug.nl; and fajri.gafar@gmail.com

**Take-home message:**

High success rates for TB treatment were achieved in children and adolescents in The Netherlands. To further optimize care in this population, several risk factors particularly associated with mortality and lost to follow-up have been identified.

**Running title:**

TB treatment outcomes in children and adolescents in The Netherlands.

**ABSTRACT**

**Background:** As a vulnerable population, children and adolescents with tuberculosis (TB) are faced with many challenges, even for those who live in low TB incidence countries. We aimed to evaluate factors associated with TB treatment outcomes allowing more focused interventions to support this population once diagnosed.

**Methods:** A retrospective cohort study using a nationwide surveillance database was performed in children and adolescents (0-18 years) treated for TB in The Netherlands from 1993-2018. Logistic regression analyses were used to estimate adjusted odds ratios (aOR) for associated factors of mortality and lost to follow-up (LTFU).

**Results:** Among 3253 eligible patients with known outcomes, 94.4% (95.9% children and 92.8% adolescents) were cured or completed treatment, 0.7% died during treatment and 4.9% were LTFU. There were no reported treatment failures. Risk factors of death included children aged 2-4 years (aOR=10.42), central nervous system TB (aOR=5.14), miliary TB (aOR=10.25), HIV coinfection (aOR=8.60), retreated TB cases (aOR=10.12), and drug-induced liver injury (aOR=6.50). Active case-finding was a protective factor of death (aOR=0.13). Risk factors of LTFU were adolescents aged 15-18 years (aOR=1.91), illegal immigrants (aOR=4.28), urban domicile (aOR=1.59), unknown history of TB contact (aOR=1.99), drug-resistant TB (aOR=2.31), single adverse drug reaction (ADR) (aOR=2.12), multiple ADRs (aOR=7.84) and treatment interruption >14 days (aOR=6.93). Treatment in recent years (aOR=0.94) and supervision by public health nurses (aOR=0.14) were protective factors of LTFU.

**Conclusion:** Highly successful treatment outcomes were demonstrated in children and adolescents routinely treated for TB. Special attention should be given to specific risk groups to improve treatment outcomes.

**Key words:** Tuberculosis, treatment outcome, mortality, lost to follow-up, children, adolescent.

## INTRODUCTION

Tuberculosis (TB) is a major global health problem with an estimated 1 million children who developed TB worldwide in 2017 [1]. Childhood TB has historically been given low priority in most national programmes because it contributes little to disease transmission. Similarly, adolescents are also faced with many challenges as they have been neglected in TB surveillance even when they suffer from a significant burden of the disease [2, 3]. Since the World Health Organization (WHO) published 10 key actions in 2013 as the first roadmap for childhood TB [4], significant progress has been made but gaps still remain especially on age- and disease-related challenges such as young children (<5 years), adolescents (10-19 years), TB/HIV coinfection, and multidrug-resistant TB (MDR-TB). The 2018 WHO roadmap brings new hope of accelerating efforts towards ending TB in children and adolescents by ensuring them to receive high priority in all TB prevention and control activities [5].

As one of the top ten causes of death, childhood TB is a silent killer with the risk of mortality being particularly high in under-five children and HIV co-infected children not receiving antiretroviral therapy (ART) [6, 7]. In low-incidence countries like The Netherlands, TB elimination requires extensive but focused screening and prevention as the patients become more concentrated in certain vulnerable and high-risk groups such as the poor, immigrants, asylum seekers, homeless, prisoners, alcohol or drug addicts, and people living with HIV/AIDS [8]. Management of childhood and adolescent TB is still a pressing challenge even for low-incidence countries, particularly due to the lack of child-friendly drug formulations, difficulties in diagnosis and treatment of latent TB infection (LTBI) [9].

Few studies with large cohorts of children mostly from high-incidence settings in Africa have reported factors associated with TB treatment outcomes in children [10–14]. However, most of the variables analysed in these studies were relatively limited to demographic and clinical characteristics. Other potential confounders such as vaccination status, types of case-finding, drug-susceptibility of the TB strains, and other clinical-, bacteriological- and treatment-related factors have not been fully evaluated. Related data in both children and adolescents from low-incidence countries is also lacking. In this context,

our study aimed to evaluate treatment outcomes and associated factors in children and adolescents routinely treated for TB in The Netherlands. This would allow for appropriate interventions to optimize TB care in this vulnerable population.

## METHODS

### Study design and data sources

This retrospective cohort study was performed using surveillance data obtained from the Netherlands Tuberculosis Register (NTR). The NTR is a nationwide database for patients with TB and LTBI, managed by the Dutch National Institute for Public Health and the Environment (RIVM) in collaboration with 25 departments of the Municipal Public Health Services (MPHS) and the Royal Netherlands Tuberculosis Association (KNCV). Since 1993, data on disease notification, demographics, clinical, bacteriological, and treatment characteristics are recorded by the MPHS in all TB patients.

### Study population

All children and adolescents (0-18 years) treated for TB between January 1993 and December 2018 were included in this study. Patients in ongoing treatment with incomplete data on treatment outcomes were excluded.

### Data collection

The following individual data with anonymous identifiers were obtained from the NTR on 22 May 2019: (1) demographics (year of diagnosis, age, gender, native/foreign-born, WHO region of birth, immigrant status, and area of living); (2) TB notification and clinical characteristics (types of case-finding, history of TB contact, travel history in TB endemic area, site and localisation of TB, cavitary TB, Bacillus Calmette-Guerin (BCG) vaccination, TB symptoms, patient's and doctor's delay in diagnosis and treatment, and comorbidity); (3) bacteriological characteristics (acid-fast bacilli (AFB) smear microscopy, mycobacterial culture, and drug susceptibility testing (DST)); and (4) treatment characteristics (previous history of TB/LTBI treatment, daily/intermittent dosing, presence of adverse drug reactions (ADRs), drug-induced liver injury (DILI), treatment interruption >14 days, hospitalisation,

treatment supervision by public health nurses (PHNs) and implementation of directly observed therapy (DOT)).

**Definitions**

Age was generally divided into 2 groups: children <15 years and adolescents aged 15-18 years. The cut-off of <15 years for children was used to be consistent with the age category used for reporting TB surveillance data nationally and by the WHO [1]. The upper age limit of 18 years for adolescent TB was based on the definition used by the WHO European Region [15]. Active case-finding (ACF) was defined as the systematic screening for active TB cases in a predetermined high-risk group for TB, rather than waiting for patients who came on their own to the healthcare system because of TB symptoms (passive case-finding (PCF)). Pulmonary TB (PTB) included all forms of TB in the lungs, isolated tracheal or bronchus TB, laryngeal TB, and other specified respiratory TB. TB within other locations in the body than the lungs, including mediastinal lymphadenopathy, were classified as extrapulmonary TB (EPTB), which may have involved isolated EPTB or a combination of PTB and EPTB. Confirmed drug-susceptible TB (DS-TB) was defined as a susceptible result of DST for all first-line anti-TB drugs (isoniazid, rifampicin, pyrazinamide and ethambutol), while presumed DS-TB was defined as patients treated with first-line anti-TB drugs without sufficient information on DST. Patients with DST results of mono-resistant, poly-resistant, MDR, or XDR (extensively drug-resistant) were classified as confirmed drug-resistant TB (DR-TB). DILI due to anti-TB drugs was defined as an increased level of alanine aminotransferase >3x the upper limit of normal (ULN) in the presence of symptoms of hepatotoxicity or >5x the ULN in the absence of symptoms. Treatment supervision by PHNs was defined as supportive discussions with patients and their family to provide TB education and identification of obstacles that influence treatment adherence. DOT was defined as every dose of anti-TB drugs taken under direct observation for a period of time, provided by either PHNs or other selected third parties such as family members or home nursing services. Operational definitions for all variables are shown in Supplementary Table 1 [16, 17].

**Outcomes**

Treatment outcomes (cured, treatment completed, died, treatment failed, lost to follow-up (LTFU), and not evaluated (unknown outcomes)) were defined based on the Dutch national guidelines for TB programmes and generally in accordance with the current WHO guidelines (Table 1) [16, 18].

**Data analysis**

Associations of patient characteristics with mortality and LTFU were evaluated. First, patients who died during treatment were compared to those who were alive at the end of treatment regardless of whether they were cured, completed or failed treatment; this definition excluded LTFU and unknown outcomes. Second, LTFU patients were compared to those who achieved cure or completed treatment with or without evidence of treatment failure; this definition excluded death and unknown outcomes. Given the possibility of selection bias from the exclusion of particular patients in the first and second analyses, additional outcome classification was created assessing patients who achieved cure or completed treatment (favourable) compared to all other outcomes (unfavourable).

Univariate and multivariate logistic regression analyses were used to evaluate the association between candidate variables and treatment outcomes. All variables in the univariate analysis showing a trend towards association with each of the evaluated outcomes, and with a minimum number of 20 patients in any particular group of predictors, were eligible for inclusion in multivariate analysis and were selected using backward elimination. The final multivariate models retained all explanatory variables with a *P*-value <0.1. The Hosmer-Lemeshow test was used to evaluate the goodness-of-fit of the final models. The performance of the final models were measured by the area under the receiver operating characteristic (ROC) curve. Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) were used to estimate the association between explanatory variables and treatment outcomes. Statistical significance was accepted at $P<0.05$ whereas *P*-values of 0.05-0.10 were considered trends. All data were analysed with IBM SPSS Statistics version 25.0.

## Ethics

Research approval was granted by the research committee of the NTR. As this was a retrospective study using routine data collected anonymously, ethics clearance and individual patient written informed consent were not required under Dutch law.

## RESULTS

During a 26-year period from January 1993 to December 2018, 3442 TB cases in children and adolescents were notified: 46 patients in ongoing treatment were excluded. Of 3396 eligible patients (1764 (51.9%) children and 1632 (48.1%) adolescents), 1893 (55.7%) being male, 2017 (59.4%) were foreign-born and 1454 (42.8%) had pulmonary TB (PTB). Mycobacterial culture was performed in 2261 (66.6%) of the eligible patients with 1921 (56.6%) being culture positive and 340 (10%) culture negative. Of 1921 patients with culture-confirmed disease, 1610 (83.8%) had information on species. Of these, 1523 (94.6%) had *M. tuberculosis* and 87 (5.4%) had other *M. tuberculosis* complex. None of the patients were identified as nontuberculous mycobacterial infections. Most of the patients (2625 (77.3%)) were treated as presumed DS-TB, 591 (17.4%) as confirmed DS-TB and 180 (5.3%) as confirmed DR-TB (Table 2). Severe forms of TB (CNS or miliary TB) were notified in 100 (2.9%) of 3396 eligible patients: 33 (33%) received BCG vaccination and 44 (44%) were BCG-unvaccinated. Of 44 severe cases who were BCG-unvaccinated, 23 (52.3%) were children <5 years, 15 (34.1%) were children aged 5-14 years and the remaining 6 (13.6%) were adolescents.

By including both patients with known and unknown outcomes, overall success rates of 92.0% and 88.7% were shown in children and adolescents, respectively. Known outcomes were recorded in 3253 (95.8%) of 3396 eligible patients. Of these, success rates were shown in 95.9% children and 92.8% adolescents (Table 2). Annual success rates in children were constantly above 90% over the years from 1993-2018, and relatively higher compared to adolescents (Figure 1). LTFU was higher in adolescents (102 (6.5%)) than children (58

(3.4%)). No treatment failure was reported and 22 (0.7%) of the total patients died during treatment (Table 2). Case fatality rates (CFR) for other sub-population are presented in Supplementary Table 2.

Our multivariate model showed that children aged 2-4 years had an increased odds of death compared to children aged 5-14 years (aOR: 10.42; 95% CI: 2.25-48.36). Positive associations with mortality were also shown in patients with central nervous system (CNS) TB (aOR: 5.14; 95% CI: 1.17-22.62), miliary TB (aOR: 10.25; 95% CI: 2.30-45.67), HIV coinfection (aOR: 8.60; 95% CI: 1.57-47.24), retreated TB cases (aOR: 10.12; 95% CI: 1.54-66.47) and those who developed DILI during therapy (aOR: 6.50; 95% CI: 1.09-38.71). The ACF was associated with lower odds of death compared to PCF (aOR: 0.13; 95% CI: 0.03-0.66) (Table 3). Patients with unknown history of TB contact, with unknown BCG status, who experienced TB symptoms or were hospitalised ≥1 week during treatment had a significant increased odds of death in univariate analysis but did not remain significant in multivariate analysis (Supplementary Table 3). Although unknown history of TB contact was not sustained in multivariate analysis as a predictor of mortality, it was significantly associated with higher odds of either patient's delay (aOR: 2.36; 95% CI: 1.46-3.80) or doctor's delay (aOR: 4.29; 95% CI: 2.48-7.42) compared to known TB contact history, adjusted for age, gender, smear microscopy and sites of TB.

Several factors were associated with higher odds of LTFU including adolescents (aOR: 1.91; 95% CI: 1.25-2.93), illegal immigrants (aOR: 4.28; 95% CI: 1.60-11.42), urban domicile (aOR: 1.59; 95% CI: 1.10-2.29), unknown history of TB contact (aOR: 1.99; 95% CI: 1.19-3.34), confirmed DR-TB (aOR: 2.31; 95% CI: 1.05-5.10), single ADR (aOR: 2.12; 95% CI: 1.18-3.83), multiple ADRs (aOR: 7.84; 95% CI: 3.55-17.33) and treatment interruption >14 days (aOR: 6.93; 95% CI: 2.72-17.63). Treatment in recent years (aOR: 0.94; 95% CI: 0.89-0.98) and treatment supervision by PHNs (aOR: 0.14; 95% CI: 0.07-0.29) were associated with lower odds of LTFU (Table 4). Being male and foreign-born were significantly associated with higher odds of LTFU in univariate analysis but not found statistically significant in multivariate analysis (Supplementary Table 4). However, our subgroup analysis

identified that male foreign-born adolescents had a significantly increased odds of LTFU compared to female foreign-born adolescents (aOR: 2.31; 95% CI: 1.30-4.10), adjusted for year of diagnosis, area of living, DST results, presence of ADRs, treatment interruption >14 days and treatment supervision by PHNs.

The following factors were associated with higher odds of unfavourable outcome: children <5 years (aOR: 1.58; 95% CI: 1.02-2.46), adolescents (aOR: 1.56; 95% CI: 1.11-2.19), illegal immigrants (aOR: 5.10; 95% CI: 2.15-12.10), unknown history of TB contact (aOR: 2.00; 95% CI: 1.30-3.07), miliary TB (aOR: 3.37; 95% CI: 1.42-8.03), multiple ADRs (aOR: 7.54; 95% CI: 3.56-15.99) and treatment interruption >14 days (aOR: 4.90; 95% CI: 2.10-11.42). Treatment supervision by PHNs was associated with lower odds of unfavourable outcome (aOR: 0.08; 95% CI: 0.05-0.15) (Table 5). Results of the univariate analysis for unfavourable outcome are presented in Supplementary Table 5.

**DISCUSSION**

An overall high success rate of 92.0% in children was recorded in our study although this included children with unknown outcomes. This is relatively comparable with studies of children from other low-incidence countries such as Australia (89.4%) and the United Kingdom (UK) (88.0%) [19, 20]. A high success rate was also recorded in adolescents: comparable data from other low-incidence countries is lacking. This underlines that adolescents are often neglected in TB surveillance reports [3, 5]. The low mortality rate of <1% in our study is similar to those reported in the UK and Australia [19, 20] but is lower compared to various reports from high-incidence countries in Asia and Africa (3-17%) [11–14]. Interestingly, a recent study from South Africa also reported less than 1% mortality rate in children; however, this number was probably higher as children with severe forms of TB admitted to hospital may have died before diagnosis or after diagnosis but prior to recording in the database [10].

Several risk factors of mortality are shown in our study including children aged 2-4 years, CNS TB, miliary TB, HIV coinfection, retreated TB cases and cases with DILI. Overall,

the increased risk of death in children under 5 years of age is consistent with those reported in a meta-analysis and a modelling study [6, 7]. However, in contrast to earlier findings from South Africa [10], our results did not confirm the risk of death in a subgroup of children <2 years. In children <2-3 years, the progression of primary infection into severe disease (CNS or miliary TB) is more frequent [21]. These severe forms of disease were associated with mortality in our study, independently from age of the patients. In high-incidence countries, BCG vaccination has been reported as a highly cost-effective intervention to prevent CNS TB and miliary TB [22]. In The Netherlands, BCG vaccination is only targeted to new-borns with a parent coming from a country with estimated TB incidence >50 per 100,000 population, and offered for immigrants <12 years with no evidence of BCG vaccination at pre-entry TB screening [23]. Notably, more patients with severe disease in our study were BCG-unvaccinated: half of them were <5 years of age. These results support the previous recommendation by Erkens et al to improve the coverage of BCG vaccination among eligible risk groups in The Netherlands [24].

The role of TB/HIV coinfection as a predictor of mortality in children is supported by various studies mostly from HIV-endemic settings [10–13]. For TB/HIV co-infected children taking antiretroviral therapy (ART), the risk of death is lower than children without ART [6]. In our cohorts, ART status was not completely clear because it was being recorded in the NTR only since 2016. Next, a recurrent episode of TB can be due to endogenous reactivation of indolent mycobacteria (relapse) or exogenous reinfection, and the latter can be caused by MDR *M. tuberculosis* strains [25]. Two patients with recurrent TB who died in our study were classified as non-relapse patients, one of which was treated for MDR-TB. It is possible that MDR-TB also plays a role in increasing the risk of mortality in recurrent TB.

DILI is one of the most frequent and serious ADRs during TB-therapy [26], and also reported as a predictor of prolonged TB treatment in a Dutch setting [27]. Although with a relatively lower rate of DILI in our study (1.8%) compared to other studies of children in Japan (8.1%) and Indonesia (15%) [28, 29], its clinical implication in increasing the risk of mortality should be taken seriously. Two studies from India and the UK also reported DILI as

a contributing cause of death in adult TB patients [30, 31], with the risk of mortality being even higher if accompanied by jaundice, ascites or encephalopathy [31]. Based on the current WHO guidelines for children, regular monitoring of liver function tests (LFTs) during TB-therapy is not mandatory and only recommended if liver tenderness, hepatomegaly, jaundice or early onset of vomiting occur during treatment [32]. Given that severe hepatotoxicity can develop in patients with asymptomatic DILI [33], regular monitoring of LFTs as suggested for adults undergoing TB therapy might also benefit children to improve treatment outcomes and to prevent mortality.

In The Netherlands, pre-entry LTBI screening is carried out for every immigrant and asylum seeker <18 years, and radiographic screening is recently suggested only in children between 12-17 years from a country with TB incidence ≥100 per 100,000 population [34]. The ACF interventions such as screening for immigrants and asylum seekers as well as source and contact investigations have proven useful in our study to prevent mortality compared to PCF. Given that unknown history of TB contact was also found as a risk factor of either patient's or doctor's delay, this highlights the benefits of advocating ACF for early diagnosis and early treatment (including preventive therapy), in order to prevent deterioration of the disease. A large randomised controlled trial (RCT) from Vietnam supports that ACF is a cost-effective intervention to increase TB case detection and to reduce all-cause mortality [35, 36]. A modelling study also reported that household contact investigations could substantially prevent both TB cases and mortality in children [37].

For LTFU, our study identifies the following risk factors: adolescent age, illegal immigrants, unknown history of TB contact, urban domicile, confirmed DR-TB, presence of ADRs and treatment interruption >14 days. The increased risk of LTFU in adolescents particularly in male foreign-born adolescents might be due to the lack of awareness of the special needs of this population [15]. To improve adherence in adolescents, appropriate interventions should be understood by considering their developmental and psychosocial issues, tailoring the treatment regimen and ensuring peer and family supports [38]. Implementation of DOT in our study was not statistically significant to prevent LTFU even in a

particular subgroup of adolescents. This is supported by a meta-analysis that poor adherence in TB treatment cannot be resolved by DOT intervention [39]. A recently published RCT from the UK reported that smartphone-enabled video-observed therapy (VOT) is more effective, preferable and cheaper than DOT for TB treatment observation [40]. In The Netherlands where internet connectivity is not an issue, VOT might also be relevant as an alternative to DOT, particularly for adolescents who have a high mobile-internet engagement. A new framework of digital health (e-health) as currently recommended by the WHO [41], might also benefit to ensure treatment adherence. Even though this e-health system has not been widely used in The Netherlands [23], it has great potential as a more patient-friendly intervention for therapy monitoring, particularly for high-risk groups and other individuals with complex confounders (e.g. patients living in urban areas or treated for DR-TB).

Since 2005, a central web-based TB surveillance system was introduced and laboratory data were matched with the NTR in real-time. These improvements might have contributed to the reduced number of LTFU cases in recent years. This is supported by our results that most of the LTFU cases (79%) were notified before 2005. The improved TB outcomes might also be related to the large number of stakeholders involved in TB control activities; from the MPHS, KNCV, RIVM, and other health professionals such as pulmonary physicians, paediatricians, TB control physicians, medical microbiologists, medical technicians and PHNs [23]. Our study confirms that treatment supervision by PHNs is a protective factor of LTFU as well as unfavourable outcome.

A particular strength of this study is a relatively wide range of variables included in the analysis from demographics to disease notification-, clinical-, bacteriological- and treatment-related factors. However, our study has several limitations that should be acknowledged. Due to the retrospective nature of the study using routine data, patient records were partly incomplete for some of the variables. Even though notification of TB is mandatory, the possibility of undernotification cases cannot be ruled out. Through a capture-recapture analysis, the adjusted undernotification of TB in 1998 was estimated to be 7.3% [42].

However, the completeness of notification is expected to have increased since 2005 when improvements were made to the NTR. The high proportion of patients with presumed DS-TB in our cohorts can be explained by these changes, given that 1139 (99%) of 1150 patients with culture-confirmed disease but did not have information on DST results were registered before 2005. Next, our database cannot distinguish between TB contact history with an infectious DR-TB and DS-TB case, and this may have led to misclassification of presumed DS-TB in some patients who should have been classified as presumed DR-TB. The low proportion of patients who died and were LTFU in our cohorts could also limit the statistical power of the study. Although the definition of mortality used in this study has followed the current WHO guidelines as all-cause mortality before starting or during the course of treatment [32], the differentiation of death due to TB from other causes along with post-mortem evidence could provide a more accurate characterisation of TB-related mortality. In addition, given the details on LFTs and clinical features of DILI are not registered in the NTR, further classification of symptomatic versus asymptomatic DILI cannot be presented.

In conclusion, this study demonstrates a high rate of successful treatment outcome in children and adolescents treated for TB in The Netherlands from 1993-2018. Specific risk groups for mortality, LTFU and unfavourable outcome have been identified for further development of early interventions to support these patients once diagnosed with TB.

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**Author contributions**

FG, NBV, BW and JWCA contributed to conception and design of the study. FG undertook data extraction and performed data analysis. FG, NBV, OWA, BW and JWCA interpreted the data. FG and NBV drafted the manuscript. BW and JWCA supervised the entire project. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript.

**Conflict of interests**

All authors do not have any conflict of interest to declare.

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Table 1. Treatment outcome definitions used in this study

| Outcomes | Definition for DS-TB | Definition for DR-TB |
|---|---|---|
| Cured | A patient who had completed a full course of therapy or at least 80% of the prescribed doses with a confirmed culture-negative at the end of treatment. | A patients who had treatment completed without evidence of failure with three or more consecutive negative cultures taken at least 30 days apart after the intensive phase |
| Treatment completed | A patient who had taken all of the prescribed doses or at least 80% of them without any information of sputum culture at the end of treatment. | A patients who had treatment completed without evidence of failure, but no record that three or more consecutive cultures taken at least 30 days apart were negative after the intensive phase |
| Died | A patient who died for any reason before starting or during the course of treatment. | A patient who died for any reason during the course of treatment |
| Treatment failed | A patient whose sputum culture was positive after 5 months or later during treatment. | A patient who met one of the following criteria: 1) lack of conversion by the end of the intensive phase, 2) bacteriological reversion in the continuation phase after conversion to negative, 3) evidence of additional acquired resistance to fluoroquinolone or second-line injectable drugs, and 4) of adverse drug reactions requiring discontinuation of treatment. |
| Lost to follow-up | A patient who met one of the following criteria: treatment interruption for two consecutive months or more; treatment completion of less than 80% of the prescribed doses; treatment incompletion of 6 months within the 9-month treatment period; or treatment incompletion of 9 months within the 12-month treatment period. | A patient whose treatment was interrupted for 2 consecutive months or more. |
| Not evaluated (Unknown) | A patient for whom no treatment outcome (cured, treatment completed, died, treatment failed, and lost to follow-up) was assigned in the database. This included cases “transferred out” to another unit (country) with unknown treatment results. | A patient for whom no treatment outcome was assigned in the database. This included cases “transferred out” to another unit (country) with unknown treatment results |
| Treatment success | The sum of “cured” and “treatment completed”. | The sum of “cured” and “treatment completed”. |

DR-TB, drug-resistant tuberculosis; DS-TB, drug-susceptible tuberculosis.
DR-TB comprised of mono-resistant TB (resistance to one first-line anti-TB drug only); poly-resistant TB (resistance to more than one first-line anti-TB drug other than isoniazid and/or rifampicin); multidrug-resistant TB (MDR-TB) (resistance to at least both isoniazid and rifampicin); extensively drug-resistant TB (resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin) in addition to MDR-TB); and rifampicin resistant TB (resistance to rifampicin with or without resistance to other anti-TB drugs). Source: [16, 18].

Table 2. Characteristics of children and adolescents treated for TB in The Netherlands

| Characteristics | Total cases (n=3396) | <5 years (n=638) | 5-14 years (n=1126) | 15-18 years (n=1632) |
|---|---|---|---|---|
| Year of diagnosis | | | | |
| 1993-1998 | 1092 (32.2) | 218 (34.2) | 400 (35.5) | 474 (29.0) |
| 1999-2003 | 1005 (29.6) | 173 (27.1) | 270 (24.0) | 562 (34.4) |
| 2004-2008 | 485 (14.3) | 110 (17.2) | 177 (15.7) | 198 (12.1) |
| 2009-2013 | 398 (11.7) | 79 (12.4) | 151 (13.4) | 168 (10.3) |
| 2014-2018 | 416 (12.2) | 58 (9.1) | 128 (11.4) | 230 (14.1) |
| Gender | | | | |
| Male | 1893 (55.7) | 337 (52.8) | 525 (46.6) | 1031 (63.2) |
| Female | 1503 (44.3) | 301 (47.2) | 601 (53.4) | 601 (36.8) |
| Born in The Netherlands | | | | |
| Yes | 1350 (39.8) | 502 (78.7) | 522 (46.4) | 326 (20.0) |
| No | 2017 (59.4) | 130 (20.4) | 594 (52.8) | 1293 (79.2) |
| Unknown | 29 (0.9) | 6 (0.9) | 10 (0.9) | 13 (0.8) |
| Site of TB | | | | |
| PTB | 1454 (42.8) | 229 (35.9) | 401 (35.6) | 824 (50.5) |
| EPTB | 1570 (46.2) | 352 (55.2) | 600 (53.3) | 618 (37.9) |
| PTB + EPTB | 372 (11.0) | 57 (8.9) | 125 (11.1) | 190 (11.6) |
| Reason for TB investigation | | | | |
| Presentation of TB symptoms | 1582 (46.6) | 178 (27.9) | 478 (42.5) | 926 (56.7) |
| Contact investigation | 944 (27.8) | 343 (53.8) | 429 (38.1) | 172 (10.5) |
| Screening high-risk groups | 620 (18.3) | 61 (9.6) | 162 (14.4) | 397 (24.3) |
| Others | 35 (1.0) | 12 (1.9) | 11 (1.0) | 12 (0.7) |
| Unknown | 215 (6.3) | 44 (6.9) | 46 (4.1) | 125 (7.7) |
| AFB smear microscopy (sputum or BAL) | | | | |
| Negative | 570 (16.8) | 51 (8.0) | 158 (14.0) | 361 (22.1) |
| Non-cavitary TB | 515 (15.2) | 48 (7.5) | 147 (13.0) | 320 (19.6) |
| Cavitary TB | 25 (0.7) | 1 (0.1) | 4 (0.3) | 20 (1.2) |
| Positive | 534 (15.7) | 26 (4.1) | 121 (10.7) | 387 (23.7) |
| Non-cavitary TB | 324 (9.5) | 23 (3.6) | 73 (6.5) | 228 (14.0) |
| Cavitary TB | 187 (5.5) | 2 (0.3) | 43 (3.8) | 142 (8.7) |
| Unknown/ not done | 2292 (67.5) | 561 (87.9) | 847 (75.2) | 884 (54.2) |
| Mycobacterial culture | | | | |
| Negative | 340 (10.0) | 60 (9.4) | 130 (11.5) | 150 (9.2) |
| Positive | 1921 (56.6) | 195 (30.6) | 506 (44.9) | 1220 (74.8) |
| Unknown/ not done | 1135 (33.4) | 383 (60.0) | 490 (43.5) | 262 (16.1) |
| Drug-susceptibility testing | | | | |
| Confirmed DS-TB | 591 (17.4) | 46 (7.2) | 144 (12.8) | 401 (24.6) |
| Presumed DS-TB | 2625 (77.3) | 568 (89.0) | 936 (83.1) | 1121 (68.7) |
| Culture positive, DST unknown | 1150 (33.9) | 125 (19.6) | 316 (28.1) | 709 (43.4) |
| Culture negative or unknown | 1475 (43.4) | 443 (69.4) | 620 (55.1) | 412 (25.2) |
| Confirmed DR-TB | 180 (5.3) | 24 (3.8) | 46 (4.1) | 110 (6.7) |
| Mono/poly H | 131 (3.9) | 20 (3.1) | 33 (2.9) | 78 (4.8) |
| Mono/poly R | 2 (0.1) | 0 (0.0) | 0 (0.0) | 2 (0.1) |
| Mono Z | 14 (0.4) | 3 (0.5) | 4 (0.4) | 7 (0.4) |
| MDR-TB | 32 (0.9) | 1 (0.2) | 9 (0.8) | 22 (1.3) |
| XDR-TB | 1 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| Treatment outcomes (uncorrected) | | | | |
| Cured/completed | 3071 (90.4) | 577 (90.4) | 1046 (92.9) | 1448 (88.7) |
| Lost to follow-up | 160 (4.7) | 24 (3.8) | 34 (3.0) | 102 (6.3) |
| Failed | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Died | 22 (0.6) | 9 (1.4) | 3 (0.3) | 10 (0.6) |
| Not evaluated (unknown) | 143 (4.2) | 28 (4.4) | 43 (3.9) | 72 (4.4) |
| Treatment outcomes (corrected)* | | | | |
| Total, n | 3253 | 610 | 1083 | 1560 |
| Cured/completed | 3071 (94.4) | 577 (94.6) | 1046 (96.6) | 1448 (92.8) |
| Lost to follow-up | 160 (4.9) | 24 (3.9) | 34 (3.1) | 102 (6.5) |
| Failed | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Died | 22 (0.7) | 9 (1.5) | 3 (0.3) | 10 (0.6) |

Data are presented as number with percentages (%); AFB, acid-fast bacilli ; BAL, bronchoalveolar lavage; DST, drug-susceptibility testing; DSTB, drug-susceptible tuberculosis; DRTB, drug-resistant tuberculosis; EPTB, extra-pulmonary tuberculosis; H, isoniazid; HIV, human immunodeficiency virus; MDR-TB, multidrug-resistant tuberculosis; PTB, pulmonary tuberculosis; R, rifampicin; XDR-TB, extensively drug-resistant tuberculosis; Z, pyrazinamide.
*Excluded patients with unknown outcomes.

Table 3. Final model for factors associated with mortality in children and adolescents treated for TB in the Netherlands

| | Died (n=22) | Alive[α] (n=3071) | cOR (95% CI) | *P*-value | aOR (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| Age | | | | | | |
| <2 years | 2 (9.1) | 220 (7.2) | 3.17 (0.53-19.08) | 0.208 | 1.22 (0.16-9.56) | 0.846 |
| 2-4 years | 7 (31.8) | 357 (11.6) | 6.84 (1.76-26.58) | 0.006 | 10.42 (2.25-48.36) | 0.003 |
| 5-14 years | 3 (13.6) | 1046 (34.1) | 1.00 | - | 1.00 | - |
| 15-18 years | 10 (45.5) | 1448 (47.2) | 2.41 (0.66-8.77) | 0.183 | 1.13 (0.27-4.77) | 0.863 |
| Type of case-finding | | | | | | |
| Passive | 15 (68.2) | 1478 (48.1) | 1.00 | - | 1.00 | - |
| Active | 2 (9.1) | 1511 (49.2) | 0.13 (0.03-0.57) | 0.007 | 0.13 (0.03-0.66) | 0.014 |
| Unknown | 5 (22.7) | 82 (2.7) | 6.01 (2.13-16.93) | 0.001 | 5.41 (1.36-21.44) | 0.016 |
| Main localisation of TB | | | | | | |
| Lungs | 8 (36.4) | 1302 (42.4) | 1.00 | - | 1.00 | - |
| CNS | 4 (18.2) | 49 (1.6) | 13.29 (3.87-45.62) | <0.001 | 5.14 (1.17-22.62) | 0.030 |
| Miliary | 6 (27.3) | 35 (1.1) | 27.90 (9.19-84.70) | <0.001 | 10.25 (2.30-45.67) | 0.002 |
| Others | 0 (0.0) | 1556 (50.7) | n/a | 0.987 | n/a | 0.986 |
| Unknown | 4 (18.2) | 129 (4.2) | 5.05 (1.50-16.99) | 0.009 | 3.51 (0.89-3.89) | 0.074 |
| HIV status | | | | | | |
| No/unknown | 18 (81.8) | 3039 (99.0) | 1.00 | - | 1.00 | - |
| HIV positive | 4 (18.2) | 32 (1.0) | 21.10 (6.76-65.86) | <0.001 | 8.60 (1.57-47.24) | 0.013 |
| Previously treated for TB | | | | | | |
| No | 13 (59.1) | 2796 (91.0) | 1.00 | - | 1.00 | - |
| Yes | 2 (9.1) | 60 (2.0) | 7.17 (1.58-32.47) | 0.011 | 10.12 (1.54-66.47) | 0.016 |
| Unknown | 7 (31.8) | 215 (7.0) | 7.00 (2.76-17.73) | <0.001 | 7.89 (2.31-26.92) | 0.001 |
| Type of ADR | | | | | | |
| No/unknown | 19 (86.4) | 2900 (94.4) | 1.00 | - | 1.00 | - |
| DILI | 2 (9.1) | 54 (1.8) | 5.65 (1.28-24.87) | 0.022 | 6.50 (1.09-38.71) | 0.040 |
| Others | 1 (4.5) | 117 (3.8) | 1.30 (0.17-9.83) | 0.796 | 0.99 (0.11-8.81) | 0.992 |

Hosmer-Lemeshow test, *P*=0.976; area under the ROC curve, 0.96 (95% CI, 0.94-0.99).
Data are presented as number with percentages (%); ADR, adverse drug reaction; aOR, adjusted odds ratio; CI, confidence interval; CNS, central nervous system; cOR, crude odds ratio; DILI, drug-induced liver injury; HIV, human immunodeficiency virus; n/a, not applicable; ROC, receiver operating characteristic.
[α]Included patients who achieved cure or completed treatment and excluded those who were LTFU or with unknown outcomes.

Table 4. Final model for factors associated with lost to follow-up in children and adolescents treated for TB in the Netherlands

| | LTFU (n=160) | Non-LTFU[£] (n=3071) | cOR (95% CI) | *P*-value | aOR (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| Year of diagnosis[#] | 1999 (1995-2003) | 2001 (1997-2009) | 0.94 (0.92-0.97) | <0.001 | 0.94 (0.89-0.98) | 0.011 |
| Age | | | | | | |
| <5 years | 24 (15.0) | 577 (18.8) | 1.28 (0.75-2.18) | 0.364 | 1.47 (0.84-2.59) | 0.178 |
| 5-14 years | 34 (21.3) | 1046 (34.1) | 1.00 | - | 1.00 | - |
| 15-18 years | 102 (63.7) | 1448 (47.2) | 2.17 (1.46-3.22) | <0.001 | 1.91 (1.25-2.93) | 0.003 |
| Immigrants or asylum seekers | | | | | | |
| No | 51 (31.9) | 1261 (41.1) | 1.00 | - | 1.00 | - |
| Yes, duration <2.5 y | 71 (44.4) | 1139 (37.1) | 1.54 (1.07-2.23) | 0.021 | 1.15 (0.73-1.81) | 0.549 |
| Yes, illegal immigrants | 8 (5.0) | 22 (0.7) | 8.99 (3.82-21.17) | <0.001 | 4.28 (1.60-11.42) | 0.004 |
| Yes, duration >2.5 y | 17 (10.6) | 502 (16.3) | 0.84 (0.48-1.46) | 0.533 | 0.59 (0.32-1.10) | 0.099 |
| Yes, duration unknown | 13 (8.1) | 147 (4.8) | 2.19 (1.16-4.12) | 0.015 | 1.32 (0.65-2.66) | 0.443 |
| Area of living | | | | | | |
| Urban[a] | 59 (36.9) | 854 (27.8) | 1.52 (1.09-2.11) | 0.014 | 1.59 (1.10-2.29) | 0.014 |
| Suburban[b] | 101 (63.1) | 2217 (72.2) | 1.00 | - | 1.00 | - |
| Known history of TB contact | | | | | | |
| No | 135 (84.4) | 2090 (68.1) | 2.53 (1.64-3.91) | <0.001 | 1.99 (1.19-3.34) | 0.009 |
| Yes | 25 (15.6) | 981 (31.9) | 1.00 | - | 1.00 | - |
| Drug susceptibility | | | | | | |
| Confirmed DS-TB | 16 (10.0) | 552 (18.0) | 1.00 | - | 1.00 | - |
| Presumed DS-TB | 127 (79.4) | 2365 (77.0) | 1.85 (1.09-3.14) | 0.022 | 1.38 (0.72-2.64) | 0.332 |
| Confirmed DR-TB | 17 (10.6) | 154 (5.0) | 3.81 (1.88-7.71) | <0.001 | 2.31 (1.05-5.10) | 0.038 |
| Presence of ADR | | | | | | |
| No/unknown | 130 (81.3) | 2900 (94.4) | 1.00 | - | 1.00 | - |
| Yes, single ADR | 19 (11.9) | 147 (4.8) | 2.88 (1.73-4.80) | <0.001 | 2.12 (1.18-3.83) | 0.012 |
| Yes, multiple ADRs | 11 (6.9) | 24 (0.8) | 10.22 (4.90-21.32) | <0.001 | 7.84 (3.55-17.33) | <0.001 |
| Treatment interruption >14 days | | | | | | |
| No | 20 (12.5) | 1045 (34.0) | 1.00 | - | 1.00 | - |
| Yes | 10 (6.3) | 42 (1.4) | 12.44 (5.48-28.23) | <0.001 | 6.93 (2.72-17.63) | <0.001 |
| Unknown | 130 (81.3) | 1984 (64.6) | 3.42 (2.13-5.51) | <0.001 | 1.03 (0.45-2.35) | 0.938 |
| Supervision by PHNs | | | | | | |
| No | 12 (7.5) | 34 (1.1) | 1.00 | - | 1.00 | - |
| Yes | 141 (88.1) | 2976 (96.9) | 0.13 (0.07-0.26) | <0.001 | 0.14 (0.07-0.29) | <0.001 |
| Unknown | 7 (4.4) | 61 (2.0) | 0.32 (0.12-0.90) | 0.031 | 0.21 (0.07-0.64) | 0.006 |

Hosmer-Lemeshow test, *P*=0.745; area under the ROC curve, 0.75 (95% CI, 0.72-0.79).
Data are presented as number with percentages (%), unless stated otherwise: [#]median with interquartile ranges (IQR); ADR, adverse drug reactions; aOR, adjusted odds ratio; CI, confidence interval; cOR, crude odds ratio; DS-TB, drug-susceptible tuberculosis; DR-TB, drug resistant tuberculosis; LTFU, lost to follow-up; PHNs, public health nurses; ROV, receiver operating characteristics; ROC, receiver operating characteristic.
[£]Included patients who achieved cure or completed treatment and excluded those who died or with unknown outcomes.
[a]The Hague, Utrecht (stad), Amsterdam and Rotterdam; [b]Groningen, Friesland, Zeeland, Drenthe, Overijssel, Gelderland, Zuid-Holland, Limburg, Utrecht, Noord-Holland, Noord-Brabant, Flevoland or other areas

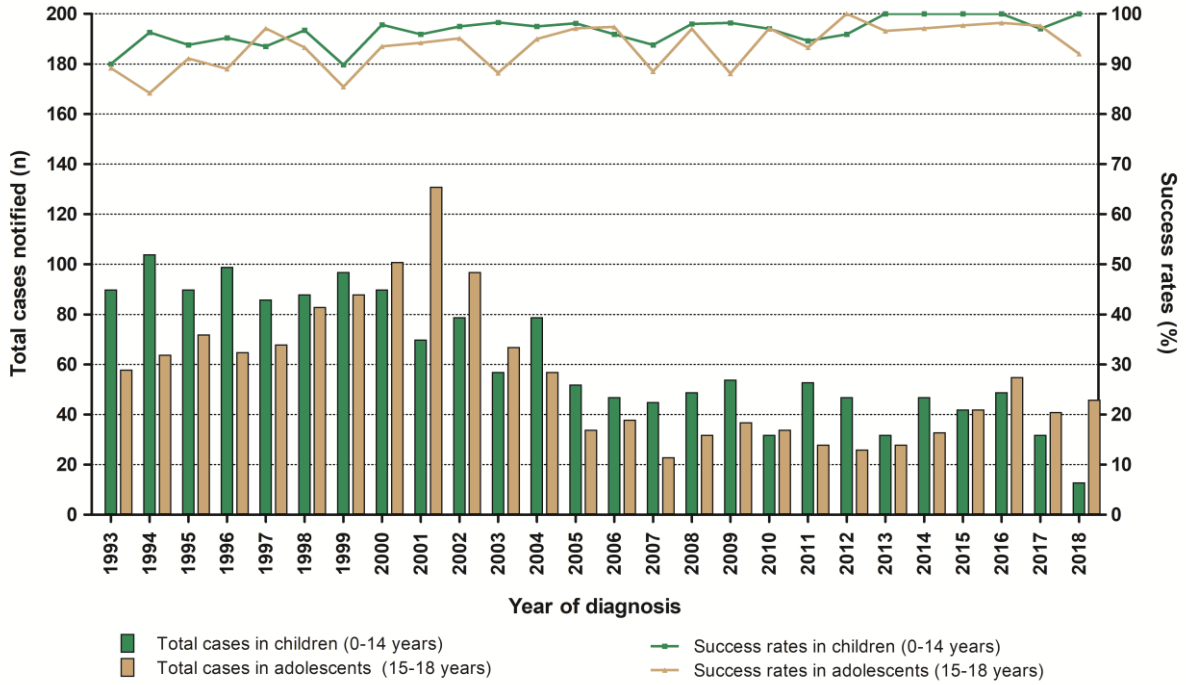
Table 5. Final model for factors associated with unfavourable outcome in children and adolescents treated for TB in the Netherlands

| | Unfavourable[¥] (n=325) | Favourable[β] (n=3071) | cOR (95% CI) | *P*-value | aOR (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| Age | | | | | | |
| <5 years | 61 (16.8) | 577 (18.8) | 1.38 (0.98-1.96) | 0.069 | 1.58 (1.02-2.46) | 0.040 |
| 5-14 years | 80 (24.6) | 1046 (34.1) | 1.00 | - | 1.00 | - |
| 15-18 years | 184 (56.6) | 1448 (47.2) | 1.66 (1.26-2.19) | <0.001 | 1.56 (1.11-2.19) | 0.010 |
| Immigrants or asylum seekers | | | | | | |
| No | 98 (30.2) | 1261 (41.1) | 1.00 | - | 1.00 | - |
| Yes, duration <2.5 y | 134 (41.2) | 1139 (37.1) | 1.51 (1.15-1.99) | 0.003 | 1.09 (0.74-1.59) | 0.663 |
| Yes, illegal immigrants | 17 (5.2) | 22 (0.7) | 9.94 (5.11-19.34) | <0.001 | 5.10 (2.15-12.10) | <0.001 |
| Yes, duration >2.5 y | 37 (11.4) | 502 (16.3) | 0.95 (0.64-1.40) | 0.791 | 0.74 (0.45-1.20) | 0.222 |
| Yes, duration unknown | 39 (12.0) | 147 (4.8) | 3.41 (2.27-5.14) | <0.001 | 1.71 (0.99-2.96) | 0.054 |
| Known TB contact history | | | | | | |
| No | 274 (84.3) | 2090 (68.1) | 2.52 (1.85-3.43) | <0.001 | 2.00 (1.30-3.07) | 0.002 |
| Yes | 51 (15.7) | 981 (31.9) | 1.00 | - | 1.00 | - |
| Main localisation of TB | | | | | | |
| Primary TB infection | 30 (9.2) | 673 (21.9) | 0.54 (0.36-0.82) | 0.004 | 0.85 (0.52-1.41) | 0.534 |
| Lungs | 107 (32.9) | 1302 (42.4) | 1.00 | - | 1.00 | - |
| Respiratory tract | 18 (5.5) | 388 (12.6) | 0.56 (0.34-0.94) | 0.029 | 0.67 (0.39-1.15) | 0.146 |
| CNS | 7 (2.2) | 49 (1.6) | 1.74 (0.77-3.93) | 0.184 | 1.52 (0.60-3.87) | 0.382 |
| Abdominal | 6 (1.8) | 51 (1.7) | 1.43 (0.60-3.41) | 0.418 | 1.81 (0.72-4.53) | 0.207 |
| Osteoarticular | 6 (1.8) | 67 (2.2) | 1.09 (0.46-2.57) | 0.844 | 1.25 (0.51-3.05) | 0.629 |
| Other organs | 33 (10.2) | 377 (12.3) | 1.06 (0.71-1.60) | 0.761 | 0.83 (0.53-1.31) | 0.427 |
| Miliary | 9 (2.8) | 35 (1.1) | 3.13 (1.46-6.68) | 0.003 | 3.37 (1.42-8.03) | 0.006 |
| Unknown | 109 (33.5) | 129 (4.2) | 10.28 (7.45-14.19) | <0.001 | 3.99 (2.56-6.20) | <0.001 |
| Previously treated for TB | | | | | | |
| No | 273 (84.0) | 2796 (91.0) | 1.00 | - | 1.00 | - |
| Yes | 13 (4.0) | 60 (2.0) | 2.22 (1.20-4.09) | 0.011 | 2.04 (0.98-4.24) | 0.057 |
| Unknown | 39 (12.0) | 215 (7.0) | 1.86 (1.29-2.67) | 0.001 | 1.07 (0.67-1.71) | 0.765 |
| Presence of ADR | | | | | | |
| No/unknown | 291 (89.5) | 2900 (94.4) | 1.00 | - | 1.00 | - |
| Yes, single ADR | 20 (6.2) | 147 (4.8) | 1.36 (0.84-2.20) | 0.216 | 1.57 (0.89-2.77) | 0.120 |
| Yes, multiple ADRs | 14 (4.3) | 24 (0.8) | 5.81 (2.97-11.36) | <0.001 | 7.54 (3.56-15.99) | <0.001 |
| Treatment interruption >14 days | | | | | | |
| No | 42 (12.9) | 1045 (34.0) | 1.00 | - | 1.00 | - |
| Yes | 11 (3.4) | 42 (1.4) | 6.52 (3.13-13.55) | <0.001 | 4.90 (2.10-11.42) | <0.001 |
| Unknown | 272 (83.7) | 1984 (64.6) | 3.41 (2.44-4.76) | <0.001 | 1.58 (1.09-2.92) | 0.016 |
| Hospitalised ≥1 week | | | | | | |
| No/ <1 week | 238 (73.2) | 2153 (70.1) | 1.00 | - | 1.00 | - |
| Yes | 68 (20.9) | 815 (26.5) | 0.75 (0.57-1.00) | 0.050 | 0.71 (0.51-1.01) | 0.055 |
| Unknown | 19 (5.8) | 103 (3.4) | 1.67 (1.01-2.77) | 0.048 | 0.86 (0.46-1.60) | 0.633 |
| Supervised by PHNs | | | | | | |
| No | 32 (9.8) | 34 (1.1) | 1.00 | - | 1.00 | - |
| Yes | 192 (59.1) | 2976 (96.9) | 0.07 (0.04-0.11) | <0.001 | 0.08 (0.05-0.15) | <0.001 |
| Unknown | 101 (31.1) | 61 (2.0) | 1.76 (0.99-3.14) | 0.055 | 1.01 (0.51-2.00) | 0.997 |

Hosmer-Lemeshow test, *P*=0.506; area under the ROC curve, 0.81 (95% CI, 0.78-0.84).
Data are presented as number (n) with percentages, unless stated otherwise: [#]median with interquartile ranges (IQR); ADR, adverse drug reactions; aOR, adjusted odds ratio; CI, confidence interval; CNS, central nervous system; cOR, crude odds ratio; HIV, human immunodeficiency virus; PHNs, public health nurses; ROC, receiver operating characteristic.
[β]The sum of patients who achieved cure or completed treatment.
[¥]The sum of patients who died, were LTFU, or with unknown outcomes

**Figure legends:**

Figure 1. Notified TB cases and trend of success rates among children and adolescents treated for TB in The Netherlands, 1993-2018



**SUPPLEMENTARY FILES:**

Supplementary table 1. Operational definitions of the explanatory variables

| Variable | Definition |
|---|---|
| **Demographic characteristics** | |
| Children | Patients aged <15 years |
| Adolescents | Patients aged 15-18 years |
| WHO Region | Six regions classified by the World Health Organisation (WHO) including African Region, Region of the Americas, South-East Asia Region, European region, Eastern Mediterranean Region, Western Pacific Region |
| Immigrant | A person who was born outside The Netherlands with a legal residence status other than tourist or refugee. |
| Non-immigrant | A native Dutch (born in The Netherlands and both parents born in The Netherlands) or a second generation immigrant (born in The Netherlands and have at least one foreign-born parent). |
| Asylum seeker | A person who has left their home country as a political refugee and is seeking asylum elsewhere. |
| Urban | Four biggest cities of the Netherlands (The Randstad) including The Hague, Utrecht, Amsterdam and Rotterdam. |
| Suburban | The province of Groningen, Friesland, Zeeland, Drenthe, Overijssel, Gelderland, Zuid-Holland, Limburg, Utrecht, Noord-Holland, Noord-Brabant, Flevoland or other areas. |
| **TB notification and clinical characteristics** | |
| Active case-finding (ACF) | The systematic screening for active TB cases in a predetermined high-risk group for TB. This included screening for immigrants and refugees, screening for detainees, hospital staff screening, screening for travellers after their journey from TB endemic areas, screening for patients diagnosed with HIV positive, TB-contact investigation, screening for homeless and drug addicts, periodic screening for health care worker or person working with TB risk groups, screening prior to immunosuppressive treatment, X-ray examination for patients with LTBI, and others (screening as a baseline measurement prior to BCG/ travel/ appointment investigation). |
| Passive case-finding (PCF) | A patient who had experienced TB symptoms (complaints) and came to the healthcare system by their own accord. |
| Known history of TB contact | A patient who had close contact history with an infectious TB case. |
| Travel history in TB endemic area >3 month | A patient who had travelled in a country with TB incidence >100 per 100,000 population for more than three months within the past two years. |
| Pulmonary TB (PTB) | All forms of TB in the lungs, isolated tracheal or bronchus TB, laryngeal TB, and other specified respiratory TB. |
| Extrapulmonary TB (EPTB) | TB within other locations in the body than the lungs, which may have included isolated EPTB or a combination of PTB and EPTB. |
| Cavitary TB | Cavitary TB involves the upper lobes of the lung and characterised by the presence of cavities in the lung tissue or enlarged air spaces. |
| BCG-vaccinated patient | A patient who had a documented medical information of vaccination history or with the presence of a Bacillus Calmette Guerin (BCG) scar |
| Had TB symptoms | A patient who had symptoms of TB disease prior to treatment. Since 2005, only “cough complaint” was recorded in the database as TB symptoms (applicable only for patients with PTB or PTB+EPTB) |
| Patient’s delay | The number of weeks (at least 1 week) from the onset of TB symptoms and the date of the first contact with health care related to this episode. |

| | |
|---|---|
| Doctor's delay | The number of weeks (at least 1 week) between the first contact with health care for TB episode and the start of TB treatment. |
| Comorbidity | Comorbidity group was composed by including patients with human immunodeficiency virus (HIV), malignancy, and other diseases (diabetes mellitus, renal insufficiency/ dialysis or organ transplantation). |
| **Bacteriological characteristics** | |
| Smear positive | The specimen from sputum, bronchoalveolar lavage (BAL) or other body materials noted as at least +1 for acid-fast bacilli (AFB+) on microscopy using Ziehl-Neelsen stain. |
| Species of Mycobacterium | Species of Mycobacterium consists of *M. tuberculosis, M. bovis*, and other *M. tuberculosis* complex such as *M. africanum, M. microti, M. canetti* or unspecified *M. tuberculosis* complex |
| Confirmed DS-TB | A patient with a susceptible result of drug-susceptibility testing (DST) for all first-line anti-TB drugs (isoniazid, rifampicin, pyrazinamide and ethambutol). |
| Presumed DS-TB | A patient treated with first-line anti-TB drugs without sufficient information on DST results |
| Confirmed DR-TB | A patient with DST results of being resistant to at least one of the fist-line TB drugs. Confirmed DR-TB was categorised as mono-resistant, poly-resistance, multidrug-resistant (MDR), or extensively drug-resistant (XDR) TB. |
| **Treatment characteristics** | |
| Retreated patient | A patient who had previously started TB treatment but was discontinued after 1 month or more. It included a patient with treatment after relapse, treatment after failure, treatment after loss to follow-up, and other previously treated cases. |
| Intermittent dosing | Anti TB-drugs dosing less than once daily during the entire course of treatment or part of the treatment. |
| Adverse drug reactions (ADRs) | Unwanted and undesirable effects of a medication defined by the treating physician, and demanding an interruption or change of the treatment regimen. ADRs included antituberculosis drug-induced liver injury (DILI), neurological disorders, mental disorders, vision disorders, drug allergy, arthralgia, and others. Any combination of ≥2 ADRs were classified as multiple ADRs. |
| Drug-induced liver injury (DILI) | DILI due to anti-TB drugs was defined as an increased levels of alanine aminotransferase >3x the upper limit of normal (ULN) in the presence of symptoms of hepatotoxicity or >5x the ULN in the absence of symptoms. |
| Treatment interruption >14 days | A patient who had interrupted treatment to more than 14 days but less than 2 months, either caused by adverse effects or other reasons. |
| Treatment supervision by public health nurses (PHNs) | Supportive discussions with patients and their family to provide TB education as well as identification of obstacles that influence treatment adherence. The intensity of supervision varies from daily to monthly contacts. |
| Directly observed therapy (DOT) | Every dose of anti-TB drugs taken under direct observation for a period of time, provided by either PHNs or other selected third parties such as family members or home nursing services |

Source: [1,2]

Supplementary table 2. Estimated case-fatality rates stratified by specific sub-population in children and adolescents treated for TB in The Netherlands, 1993-2018

| | [α]Total, n | Deaths, n | CFR (95% CI) |
|---|---|---|---|
| Total patients | 3093 | 22 | 0.7 (0.4-1.1) |
| Stratified by age | | | |
| 0-4 years | 586 | 9 | 1.5 (0.7-2.9) |
| 5-14 years | 1049 | 3 | 0.3 (0.1-0.8) |
| 15-18 years | 1458 | 10 | 0.7 (0.3-1.3) |
| Stratified by DST | | | |
| Confirmed DS-TB | 558 | 6 | 1.1 (0.4-2.3) |
| Presumed DS-TB | 2379 | 14 | 0.6 (0.3-1.0) |
| Confirmed DR-TB | 156 | 2 | 1.3 (0.2-4.6) |
| Stratified by HIV(+) and age | | | |
| HIV(+) aged 0-4 years | 4 | 1 | 25.0 (0.6-80.6) |
| HIV(+) aged 5-14 years | 10 | 0 | 0.0 (0.0-33.6) |
| HIV(+) aged 15-18 years | 23 | 3 | 13.0 (2.8-33.6) |
| Stratified by TB localisation | | | |
| Lungs | 1310 | 8 | 0.6 (0.3-1.2) |
| CNS | 53 | 4 | 7.5 (2.1-18.2) |
| Miliary | 41 | 6 | 14.6 (5.6-29.2) |
| Stratified by BCG vaccination and age | | | |
| BCG-unvaccinated, aged 0-4 years | 405 | 3 | 0.7 (0.2-2.1) |
| BCG-unvaccinated, aged 5-14 years | 468 | 1 | 0.2 (0.0-1.2) |
| BCG-unvaccinated, aged 15-18 years | 299 | 1 | 0.3 (0.0-1.8) |

Abbreviations: BCG, Bacillus Calmette-Guerin; CFR, case fatality rate; CI, confidence interval; CNS, central nervous system; DST, drug-susceptibility testing; DS-TB, drug-susceptible tuberculosis; DR-TB, drug-resistant tuberculosis; HIV, human immunodeficiency virus.

[α]Included patients who were cured, completed treatment or died; and excluded those who were LTFU or with unknown outcomes.

Supplementary table 3. Factors associated with mortality in children and adolescents treated for TB in the Netherlands using univariate logistic regression analysis

| | Died (n=22) | Alive[α] (n=3071) | OR (95% CI) | *P*-value |
|---|---|---|---|---|
| Demographic characteristics | | | | |
| Year of diagnosis[#] | 2001 (1996-2004) | 2001 (1997-2009) | 0.95 (0.89-1.01) | 0.117 |
| Year of diagnosis | | | | |
| 1993-1998 | 9 (40.9) | 967 (31.5) | 1.00 | |
| 1999-2003 | 7 (31.8) | 877 (28.6) | 0.86 (0.32-2.31) | 0.761 |
| 2004-2008 | 4 (18.2) | 456 (14.8) | 0.94 (0.29-3.08) | 0.922 |
| 2009-2013 | 2 (9.1) | 371 (12.1) | 0.58 (0.12-2.69) | 0.486 |
| 2014-2018 | 0 (0.0) | 400 (13.0) | n/a | 0.993 |
| [a]Age | | | | |
| <2 years | 2 (9.1) | 220 (7.2) | 3.17 (0.53-19.08) | 0.208 |
| 2-4 years | 7 (31.8) | 357 (11.6) | 6.84 (1.76-26.58) | 0.006 |
| 5-14 years | 3 (13.6) | 1046 (34.1) | 1.00 | - |
| 15-18 years | 10 (45.5) | 1448 (47.2) | 2.41 (0.66-8.77) | 0.183 |
| Gender | | | | |
| Male | 12 (54.5) | 1690 (55.0) | 0.98 (0.42-2.28) | 0.981 |
| Female | 10 (45.5) | 1381 (45.0) | 1.00 | |
| Born in The Netherlands | | | | |
| Yes | 7 (31.8) | 1252 (40.8) | 1.00 | |
| No | 15 (68.2) | 1795 (58.5) | 1.49 (0.61-3.68) | 0.381 |
| Unknown | 0 (0.0) | 24 (0.8) | n/a | 0.998 |
| WHO Region of birth | | | | |
| European | 8 (36.4) | 1362 (44.4) | 1.00 | |
| African | 7 (31.8) | 565 (18.4) | 2.11 (0.76-5.84) | 0.151 |
| Eastern Mediterranean | 6 (27.3) | 879 (28.6) | 1.16 (0.40-3.36) | 0.782 |
| Other regions | 1 (4.5) | 241 (7.8) | 0.71 (0.09-5.67) | 0.744 |
| Unknown | 0 (0.0) | 24 (0.8) | n/a | 0.998 |
| [a]Immigrants or asylum seekers | | | | |
| No | 7 (31.8) | 1261 (41.1) | 1.00 | |
| Yes, duration <2.5 y | 5 (22.7) | 1139 (37.1) | 0.79 (0.25-2.50) | 0.698 |
| Yes, illegal immigrants | 1 (4.5) | 22 (0.7) | 8.19 (0.97-69.41) | 0.054 |
| Yes, duration >2.5 y | 5 (22.7) | 502 (16.3) | 1.79 (0.57-5.68) | 0.320 |
| Yes, duration unknown | 4 (18.2) | 147 (4.8) | 4.90 (1.42-16.94) | 0.012 |
| Area of living | | | | |
| Urban | 4 (18.2) | 854 (27.8) | 1.00 | |
| Suburban | 18 (81.8) | 2217 (72.2) | 1.73 (0.58-5.14) | 0.321 |
| TB notification and clinical characteristics | | | | |
| [a]Type of case finding | | | | |
| Passive | 15 (68.2) | 1478 (48.1) | 1.00 | |
| Active | 2 (9.1) | 1511 (49.2) | 0.13 (0.03-0.57) | 0.007 |
| Unknown | 5 (22.7) | 82 (2.7) | 6.01 (2.13-16.93) | 0.001 |
| [a]Known TB contacts | | | | |
| No | 21 (95.5) | 2090 (68.1) | 9.86 (1.32-73.38) | 0.025 |
| Yes | 1 (4.5) | 981 (31.9) | 1.00 | |
| Travelling in TB endemic area >3 months | | | | |
| No | 21 (95.5) | 3044 (99.1) | 1.00 | |
| Yes | 1 (4.5) | 27 (0.9) | 5.37 (0.70-41.35) | 0.107 |
| [a,b]Site of TB disease | | | | |
| PTB | 7 (31.8) | 1291 (42.0) | 1.00 | |
| EPTB | 3 (13.6) | 1452 (47.3) | 0.38 (0.10-1.48) | 0.163 |
| PTB + EPTB | 12 (54.5) | 328 (10.7) | 6.75 (2.64-17.27) | <0.001 |
| [a,b]Main localisation of TB | | | | |
| Lungs | 8 (36.4) | 1302 (42.4) | 1.00 | |
| CNS | 4 (18.2) | 49 (1.6) | 13.29 (3.87-45.62) | <0.001 |
| Miliary | 6 (27.3) | 35 (1.1) | 27.90 (9.19-84.70) | <0.001 |

| | | | | |
|---|---|---|---|---|
| Others | 0 (0.0) | 1556 (50.7) | n/a | 0.987 |
| Unknown | 4 (18.2) | 129 (4.2) | 5.05 (1.50-16.99) | 0.009 |
| Cavitary TB | | | | |
| No | 15 (68.2) | 2711 (88.3) | 1.00 | |
| Yes | 3 (13.6) | 231 (7.5) | 2.35 (0.67-8.17) | 0.180 |
| Unknown | 4 (18.2) | 129 (4.2) | 5.60 (1.83-17.12) | 0.002 |
| [a]BCG-vaccinated | | | | |
| Yes | 6 (27.3) | 1163 (37.9) | 1.00 | |
| No | 5 (22.7) | 1167 (38.0) | 0.83 (0.25-2.73) | 0.760 |
| Unknown | 11 (50.0) | 741 (24.1) | 2.88 (1.06-7.81) | 0.038 |
| [a]Had TB symptoms | | | | |
| No | 1 (4.5) | 930 (30.3) | 1.00 | |
| Yes | 19 (86.4) | 1688 (55.0) | 10.47 (1.40-78.32) | 0.022 |
| Unknown | 2 (9.1) | 453 (14.8) | 4.10 (0.37-45.40) | 0.249 |
| Patient's delay | | | | |
| No | 1 (4.5) | 781 (25.4) | 1.00 | |
| Yes, >1 week | 6 (27.3) | 1001 (32.6) | 4.68 (0.56-38.96) | 0.153 |
| Unknown | 15 (68.2) | 1289 (42.0) | 9.09 (1.20-68.94) | 0.033 |
| Doctor's delay | | | | |
| No | 4 (18.2) | 577 (18.8) | 1.00 | |
| Yes, >1 week | 6 (27.3) | 930 (30.3) | 0.93 (0.26-3.31) | 0.912 |
| Unknown | 12 (54.5) | 1564 (50.9) | 1.11 (0.36-3.44) | 0.861 |
| Total delay (doctor + patient) | | | | |
| No | 1 (4.5) | 103 (3.4) | 1.00 | |
| Yes, >1 week | 5 (22.7) | 952 (31.0) | 0.54 (0.06-4.67) | 0.577 |
| Unknown | 16 (72.7) | 2016 (65.6) | 0.82 (0.11-6.22) | 0.846 |
| [a]Comorbidity | | | | |
| No/unknown | 16 (72.7) | 3031 (98.7) | 1.00 | |
| HIV positive | 4 (18.2) | 32 (1.0) | 23.68 (7.50-74.76) | <0.001 |
| Malignancy[μ] | 2 (9.1) | 4 (0.1) | 94.72 (16.18-554.44) | <0.001 |
| Others[μ] | 0 (0.0) | 4 (0.1) | n/a | 0.999 |
| Bacteriological characteristics | | | | |
| Sputum smear microscopy | | | | |
| Negative | 3 (13.6) | 480 (15.6) | 1.00 | |
| Positive | 8 (36.4) | 433 (14.1) | 2.96 (0.78-11.21) | 0.111 |
| Unknown/ not done | 11 (50.0) | 2158 (70.3) | 0.82 (0.23-2.93) | 0.755 |
| BAL smear microscopy | | | | |
| Negative | 2 (9.1) | 109 (3.5) | 1.00 | |
| Positive | 5 (22.7) | 104 (3.4) | 2.62 (0.50-13.80) | 0.256 |
| Unknown/ not done | 15 (68.2) | 2858 (93.1) | 0.29 (0.06-1.27) | 0.099 |
| Mycobacterial culture | | | | |
| Negative | 1 (4.5) | 319 (10.4) | 1.00 | |
| Positive | 18 (81.8) | 1734 (56.5) | 3.31 (0.44-24.89) | 0.245 |
| Unknown/ not done | 3 (13.6) | 1018 (33.1) | 0.94 (0.10-9.07) | 0.957 |
| Species of Mycobacterium | | | | |
| *M. tuberculosis* | 17 (77.3) | 1372 (44.7) | 1.00 | |
| Other *M. tuberculosis* complex | 1 (4.5) | 79 (2.6) | 1.02 (0.13-7.77) | 0.984 |
| Unknown | 4 (18.2) | 1620 (52.8) | 0.20 (0.07-0.59) | 0.004 |
| Drug susceptibility | | | | |
| Confirmed DS-TB | 6 (27.3) | 552 (18.0) | 1.00 | |
| Presumed DS-TB | 14 (63.6) | 2365 (77.0) | 0.54 (0.21-1.42) | 0.215 |
| Confirmed DR-TB | 2 (9.1) | 154 (5.0) | 1.19 (0.24-5.98) | 0.828 |
| Treatment characteristics | | | | |
| [a]Previously treated for TB | | | | |
| No | 13 (59.1) | 2796 (91.0) | 1.00 | |
| Yes | 2 (9.1) | 60 (2.0) | 7.17 (1.58-32.47) | 0.011 |
| Unknown | 7 (31.8) | 215 (7.0) | 7.00 (2.76-17.73) | <0.001 |
| Previously treated for LTBI | | | | |
| No | 3 (13.6) | 970 (31.6) | 1.00 | |
| Yes | 0 (0.0) | 78 (2.5) | n/a | 0.997 |

| | | | | |
|---|---|---|---|---|
| Unknown | 19 (86.4) | 2023 (65.9) | 3.04 (0.90-10.29) | 0.074 |
| Drug dosing schedule | | | | |
| Daily | 5 (22.7) | 1085 (35.3) | 1.00 | |
| Intermittent[μ] | 0 (0.0) | 7 (0.2) | n/a | 0.999 |
| Unknown | 17 (77.3) | 1979 (64.4) | 1.86 (0.69-5.07) | 0.222 |
| [a,c]Presence of ADR | | | | |
| No/unknown | 19 (86.4) | 2900 (94.4) | 1.00 | |
| Yes, single ADR | 1 (4.5) | 147 (4.8) | 1.04 (0.14-7.81) | 0.971 |
| Yes, multiple ADRs | 2 (9.1) | 24 (0.8) | 12.72 (2.81-57.66) | 0.001 |
| [a,c]Type of ADR | | | | |
| No/unknown | 19 (86.4) | 2900 (94.4) | 1.00 | |
| DILI | 2 (9.1) | 54 (1.8) | 5.65 (1.28-24.87) | 0.022 |
| Others | 1 (4.5) | 117 (3.8) | 1.30 (0.17-9.83) | 0.796 |
| Treatment interruption >14 days | | | | |
| No | 4 (18.2) | 1045 (34.0) | 1.00 | |
| Yes | 0 (0.0) | 42 (1.4) | n/a | 0.998 |
| Unknown | 18 (81.8) | 1984 (64.6) | 2.37 (0.80-7.02) | 0.119 |
| [a]Hospitalised ≥1 week | | | | |
| No/ <1 week | 8 (36.4) | 2153 (70.1) | 1.00 | |
| Yes | 10 (45.5) | 815 (26.5) | 3.30 (1.30-8.40) | 0.012 |
| Unknown | 4 (18.2) | 103 (3.4) | 10.45 (3.10-35.27) | <0.001 |
| DOT | | | | |
| Yes | 6 (27.3) | 827 (26.9) | 1.00 | |
| No | 16 (72.7) | 2240 (72.9) | 0.98 (0.38-2.52) | 0.974 |
| Unknown | 0 (0.0) | 4 (0.1) | n/a | 0.999 |

Data are presented as number (n) with percentages (%), unless stated otherwise: [#]median with interquartile ranges (IQR).

Abbreviations: ACF, active case finding ; ADR, adverse drug reactions; BAL, bronchoalveolar lavage; BCG, Bacillus Calmette-Guerin; CI, confidence interval; CNS, central nervous system; DILI, drug-induced liver injury; DOT, directly observed therapy; DS-TB, drug-susceptible tuberculosis; DR-TB, drug-resistant tuberculosis; E, ethambutol; EPTB, extra-pulmonary tuberculosis; H, isoniazid; HIV, human immunodeficiency virus; LTBI, latent tuberculosis infection; n/a, not applicable; OR, odds ratio; PCF, passive case finding; PTB, pulmonary tuberculosis; R, rifampicin; Z, pyrazinamide.

[α]Included patients who achieved cure or completed treatment and excluded those who were LTFU or with unknown outcomes.

[a]Variables eligible for inclusion in multivariate analysis.

[b,c]Due to the likelihood of collinearity, only one of each of these variables was included during the development of the final multivariate model.

[μ]Excluded from multivariate analysis due to the low number of patients (<20).

Supplementary table 4. Factors associated with lost to follow-up in children and adolescents treated for TB in The Netherlands using univariate logistic regression analysis

| | LTFU (n=160) | Non-LTFU[£] (n=3071) | OR (95% CI) | *P*-value |
|---|---|---|---|---|
| Demographic characteristics | | | | |
| [a,b]Year of diagnosis[#] | 1999 (1995-2003) | 2001 (1997-2009) | 0.94 (0.92-0.97) | <0.001 |
| [a,b]Year of diagnosis | | | | |
| 1993-1998 | 67 (41.9) | 967 (31.5) | 1.00 | |
| 1999-2003 | 56 (35.0) | 877 (28.6) | 0.92 (0.64-1.33) | 0.662 |
| 2004-2008 | 14 (8.8) | 456 (14.8) | 0.44 (0.25-0.80) | 0.007 |
| 2009-2013 | 14 (8.8) | 371 (12.1) | 0.54 (0.30-0.98) | 0.043 |
| 2014-2018 | 9 (5.6) | 400 (13.0) | 0.32 (0.16-0.66) | 0.002 |
| [a]Age | | | | |
| <5 years | 24 (15.0) | 577 (18.8) | 1.28 (0.75-2.18) | 0.364 |
| 5-14 years | 34 (21.3) | 1046 (34.1) | 1.00 | |
| 15-18 years | 102 (63.7) | 1448 (47.2) | 2.17 (1.46-3.22) | <0.001 |
| [a]Gender | | | | |
| Male | 101 (63.1) | 1690 (55.0) | 1.40 (1.01-1.94) | 0.045 |
| Female | 59 (36.9) | 1381 (45.0) | 1.00 | |
| [a,c]Born in The Netherlands | | | | |
| Yes | 52 (32.5) | 1252 (40.8) | | |
| No | 108 (67.5) | 1795 (58.5) | 1.45 (1.03-2.03) | 0.032 |
| Unknown | 0 (0.0) | 24 (0.8) | n/a | 0.998 |
| [a,c]WHO Region of birth | | | | |
| European | 64 (40.0) | 1362 (44.4) | 1.00 | |
| African | 28 (17.5) | 565 (18.4) | 1.05 (0.67-1.66) | 0.819 |
| Eastern Mediterranean | 57 (35.6) | 879 (28.6) | 1.38 (0.96-1.99) | 0.085 |
| Americas | 0 (0.0) | 56 (1.8) | n/a | 0.997 |
| South-East Asian | 2 (1.3) | 79 (2.6) | 0.54 (0.13-2.24) | 0.395 |
| Western Pacific | 9 (5.6) | 105 (3.4) | 1.82 (0.88-3.77) | 0.104 |
| Unknown | 0 (0.0) | 25 (0.8) | n/a | 0.998 |
| [a]Immigrants or asylum seekers | | | | |
| No | 51 (31.9) | 1261 (41.1) | 1.00 | |
| Yes, duration <2.5 y | 71 (44.4) | 1139 (37.1) | 1.54 (1.07-2.23) | 0.021 |
| Yes, illegal immigrants | 8 (5.0) | 22 (0.7) | 8.99 (3.82-21.17) | <0.001 |
| Yes, duration >2.5 y | 17 (10.6) | 502 (16.3) | 0.84 (0.48-1.46) | 0.533 |
| Yes, duration unknown | 13 (8.1) | 147 (4.8) | 2.19 (1.16-4.12) | 0.015 |
| [a]Area of living | | | | |
| Urban | 59 (36.9) | 854 (27.8) | 1.52 (1.09-2.11) | 0.014 |
| Suburban | 101 (63.1) | 2217 (72.2) | 1.00 | |
| TB notification and clinical characteristics | | | | |
| Type of case finding | | | | |
| Passive | 85 (53.1) | 1478 (48.1) | 1.00 | |
| Active | 66 (41.3) | 1511 (49.2) | 0.76 (0.55-1.06) | 0.102 |
| Unknown | 9 (5.6) | 82 (2.7) | 1.91 (0.93-3.93) | 0.079 |
| [a]Known TB contacts | | | | |
| No | 135 (84.4) | 2090 (68.1) | 2.53 (1.64-3.91) | <0.001 |
| Yes | 25 (15.6) | 981 (31.9) | 1.00 | |
| Travelling in TB endemic area >3 months | | | | |
| No | 158 (98.8) | 3044 (99.1) | 1.00 | |
| Yes | 2 (1.3) | 27 (0.9) | 1.43 (0.34-6.05) | 0.630 |
| Site of TB disease | | | | |
| PTB | 67 (41.9) | 1291 (42.0) | 1.00 | |
| EPTB | 71 (44.4) | 1452 (47.3) | 0.94 (0.67-1.33) | 0.733 |
| PTB + EPTB | 22 (13.8) | 328 (10.7) | 1.29 (0.79-2.12) | 0.311 |
| [a]Main localisation of TB | | | | |
| Primary TB infection | 21 (13.1) | 673 (21.9) | 0.56 (0.34-0.93) | 0.023 |
| Lungs | 72 (45.0) | 1302 (42.4) | 1.00 | |

| | | | | |
|---|---|---|---|---|
| Respiratory tract | 16 (10.0) | 388 (12.6) | 0.75 (0.43-1.30) | 0.299 |
| CNS | 1 (0.6) | 49 (1.6) | 0.37 (0.05-2.71) | 0.327 |
| Abdominal | 4 (2.5) | 51 (1.7) | 1.42 (0.50-4.03) | 0.512 |
| Osteoarticular | 5 (3.1) | 67 (2.2) | 1.35 (0.53-3.45) | 0.532 |
| Other organs | 24 (15.0) | 377 (12.3) | 1.15 (0.71-1.85) | 0.562 |
| Miliary | 2 (1.3) | 35 (1.1) | 1.03 (0.24-4.38) | 0.965 |
| Unknown | 15 (9.4) | 129 (4.2) | 2.10 (1.17-3.77) | 0.013 |
| Cavitary TB | | | | |
| No | 132 (82.5) | 2711 (88.3) | 1.00 | |
| Yes | 13 (8.1) | 231 (7.5) | 1.16 (0.64-2.07) | 0.628 |
| Unknown | 15 (9.4) | 129 (4.2) | 2.39 (1.36-4.19) | 0.002 |
| BCG-vaccinated | | | | |
| Yes | 58 (36.3) | 1163 (37.9) | 1.00 | |
| No | 52 (32.5) | 1167 (38.0) | 0.89 (0.61-1.31) | 0.564 |
| Unknown | 50 (31.3) | 741 (24.1) | 1.35 (0.92-2.00) | 0.128 |
| Had TB symptoms | | | | |
| No | 49 (30.6) | 930 (30.3) | 1.00 | |
| Yes | 93 (58.1) | 1688 (55.0) | 1.05 (0.73-1.49) | 0.805 |
| Unknown | 18 (11.3) | 453 (14.8) | 0.75 (0.43-1.31) | 0.316 |
| Patient's delay | | | | |
| No | 46 (28.7) | 781 (25.4) | 1.00 | |
| Yes, 1-4 weeks | 25 (15.6) | 608 (19.8) | 0.70 (0.42-1.15) | 0.158 |
| Yes, 5-8 weeks | 12 (7.5) | 168 (5.5) | 1.21 (0.63-2.34) | 0.565 |
| Yes, >8 weeks | 11 (6.9) | 225 (7.3) | 0.83 (0.42-1.63) | 0.588 |
| Unknown | 66 (41.3) | 1289 (42.0) | 0.87 (0.59-1.28) | 0.478 |
| Doctor's delay | | | | |
| No | 33 (20.6) | 577 (18.8) | 1.00 | |
| Yes, 1-4 weeks | 33 (20.6) | 556 (18.1) | 1.04 (0.63-1.70) | 0.884 |
| Yes, 5-8 weeks | 10 (6.3) | 137 (4.5) | 1.28 (0.61-2.65) | 0.513 |
| Yes, >8 weeks | 12 (7.5) | 237 (7.7) | 0.88 (0.45-1.74) | 0.725 |
| Unknown | 72 (45.0) | 1564 (50.9) | 0.80 (0.53-1.23) | 0.315 |
| Total delay (doctor + patient) | | | | |
| No | 6 (3.8) | 103 (3.4) | 1.00 | |
| Yes, 1-4 weeks | 23 (14.4) | 332 (10.8) | 1.19 (0.47-3.00) | 0.714 |
| Yes, 5-8 weeks | 9 (5.6) | 206 (6.7) | 0.75 (0.26-2.16) | 0.595 |
| Yes, >8 weeks | 24 (15.0) | 414 (13.5) | 0.99 (0.40-2.50) | 0.992 |
| Unknown | 98 (61.3) | 2016 (65.6) | 0.83 (0.36-1.95) | 0.676 |
| Comorbidity | | | | |
| No/unknown | 158 (98.8) | 3031 (98.7) | 1.00 | |
| HIV positive | 0 (0.0) | 32 (1.0) | n.a | 0.998 |
| Malignancy | 1 (0.6) | 4 (0.1) | 4.80 (0.53-43.16) | 0.162 |
| Others | 1 (0.6) | 4 (0.1) | 4.80 (0.53-43.16) | 0.162 |
| Bacteriological characteristics | | | | |
| Sputum smear microscopy | | | | |
| Negative | 25 (15.6) | 480 (15.6) | 1.00 | |
| Positive | 18 (11.3) | 433 (14.1) | 0.80 (0.43-1.48) | 0.476 |
| Unknown/ not done | 117 (73.1) | 2158 (70.3) | 1.04 (0.67-1.62) | 0.859 |
| BAL smear microscopy | | | | |
| Negative | 6 (3.8) | 109 (3.5) | 1.00 | |
| Positive | 3 (1.9) | 104 (3.4) | 0.52 (0.13-2.15) | 0.370 |
| Unknown/ not done | 151 (94.4) | 2858 (93.1) | 0.96 (0.41-2.22) | 0.924 |
| Mycobacterial culture | | | | |
| Negative | 13 (8.1) | 319 (10.4) | 1.00 | |
| Positive | 104 (65.0) | 1734 (56.5) | 1.47 (0.82-2.65) | 0.198 |
| Unknown/ not done | 43 (26.9) | 1018 (33.1) | 1.04 (0.55-1.95) | 0.912 |
| Species of Mycobacterium | | | | |
| *M. tuberculosis* | 77 (48.1) | 1372 (44.7) | 1.00 | |
| Other *M. tuberculosis* complex | 4 (2.5) | 79 (2.6) | 0.90 (0.32-2.53) | 0.845 |
| Unknown | 79 (49.4) | 1620 (52.8) | 0.87 (0.63-0.20) | 0.392 |
| [a]Drug susceptibility | | | | |

| | | | | |
|---|---|---|---|---|
| Confirmed DS-TB | 16 (10.0) | 552 (18.0) | 1.00 | |
| Presumed DS-TB | 127 (79.4) | 2365 (77.0) | 1.85 (1.09-3.14) | 0.022 |
| Confirmed DR-TB | 17 (10.6) | 154 (5.0) | 3.81 (1.88-7.71) | <0.001 |
| Treatment characteristics | | | | |
| Previously treated for TB | | | | |
| No | 140 (87.5) | 2796 (91.0) | 1.00 | |
| Yes | 6 (3.8) | 60 (2.0) | 2.00 (0.85-4.70) | 0.113 |
| Unknown | 14 (8.8) | 215 (7.0) | 1.30 (0.74-2.29) | 0.363 |
| Previously treated for LTBI | | | | |
| No | 29 (18.1) | 970 (31.6) | 1.00 | |
| Yes | 3 (1.9) | 78 (2.5) | 1.29 (0.38-4.32) | 0.683 |
| Unknown | 128 (80.0) | 2023 (65.9) | 2.12 (1.40-3.19) | <0.001 |
| [a]Drug dosing schedule | | | | |
| Daily | 30 (18.8) | 1085 (35.3) | 1.00 | |
| Intermittent[μ] | 3 (1.9) | 7 (0.2) | 15.50 (3.82-62.87) | <0.001 |
| Unknown | 127 (79.4) | 1979 (64.4) | 2.32 (1.55-3.48) | <0.001 |
| [a,d]Presence of ADR | | | | |
| No/unknown | 130 (81.3) | 2900 (94.4) | 1.00 | |
| Yes, single ADR | 19 (11.9) | 147 (4.8) | 2.88 (1.73-4.80) | <0.001 |
| Yes, multiple ADRs | 11 (6.9) | 24 (0.8) | 10.22 (4.90-21.32) | <0.001 |
| [a,d]Type of ADR | | | | |
| No/unknown | 130 (81.3) | 2900 (94.4) | 1.00 | |
| DILI | 7 (4.4) | 54 (1.8) | 2.89 (1.29-6.48) | 0.010 |
| Others | 23 (14.4) | 117 (3.8) | 4.38 (2.71-7.09) | <0.001 |
| [a]Treatment interruption >14 days | | | | |
| No | 20 (12.5) | 1045 (34.0) | 1.00 | |
| Yes | 10 (6.3) | 42 (1.4) | 12.44 (5.48-28.23) | <0.001 |
| Unknown | 130 (81.3) | 1984 (64.6) | 3.42 (2.13-5.51) | <0.001 |
| Hospitalised ≥1 week | | | | |
| No/ <1 week | 106 (66.3) | 2153 (70.1) | 1.00 | |
| Yes | 42 (26.3) | 815 (26.5) | 1.05 (0.73-1.51) | 0.807 |
| Unknown | 12 (7.5) | 103 (3.4) | 2.37 (1.26-4.44) | 0.007 |
| [a]Supervised by PHNs | | | | |
| No | 12 (7.5) | 34 (1.1) | 1.00 | |
| Yes | 141 (88.1) | 2976 (96.9) | 0.13 (0.07-0.26) | <0.001 |
| Unknown | 7 (4.4) | 61 (2.0) | 0.32 (0.12-0.90) | 0.031 |
| [a]DOT | | | | |
| Yes | 32 (20.0) | 827 (26.9) | 1.00 | |
| No | 127 (79.4) | 2240 (72.9) | 1.46 (0.99-2.18) | 0.059 |
| Unknown | 1 (0.6) | 4 (0.1) | 6.46 (0.70-59.46) | 0.099 |

Data are presented as number (n) with percentages, unless stated otherwise: [#]median with interquartile ranges (IQR).

Abbreviations: ADR, adverse drug reactions; BAL, bronchoalveolar lavage; BCG, Bacillus Calmette Guerin; CI, confidence interval; CNS, central nervous system; DILI, drug-induced liver injury; DOT, directly observed therapy; DS-TB, drug-susceptible tuberculosis; DR-TB, drug-resistant tuberculosis; E, ethambutol; EPTB, extra-pulmonary tuberculosis; H, isoniazid; HIV, human immunodeficiency virus; LTFU, lost to follow-up; LTBI, latent tuberculosis infection; n/a, not applicable; OR, odds ratio; PHNs, public health nurses; PTB, pulmonary tuberculosis; R, rifampicin; Z, pyrazinamide.

[£]Included patients who achieved cure or completed treatment and excluded those who died or with unknown outcomes.

[a]Variable eligible for inclusion in multivariate analysis.

[b,c,d]Due to the likelihood of collinearity, only one of each of these variables was included during the development of the final multivariate model.

[μ]Excluded from multivariate analysis due to the low number of patients (<20).

Supplementary table 5. Factors associated with unfavourable outcome in children and adolescents treated for TB in The Netherlands using univariate logistic regression analysis

| | Unfavourable[¥] (n=325) | Favourable[ß] (n=3071) | OR (95% CI) | *P*-value |
|---|---|---|---|---|
| Demographic characteristics | | | | |
| [a,b]Year of diagnosis[#] | 2000 (1995-2003) | 2001 (1997-2009) | 0.95 (0.93-0.96) | <0.001 |
| [a,b]Year of diagnosis | | | | |
| 1993-1998 | 125 (38.5) | 967 (31.5) | 1.00 | |
| 1999-2003 | 128 (39.4) | 877 (28.6) | 1.13 (0.87-1.47) | 0.365 |
| 2004-2008 | 29 (8.9) | 456 (14.8) | 0.49 (0.32-0.75) | 0.001 |
| 2009-2013 | 27 (8.3) | 371 (12.1) | 0.56 (0.36-0.87) | 0.009 |
| 2014-2018 | 16 (4.9) | 400 (13.0) | 0.31 (0.18-0.53) | <0.001 |
| [a]Age | | | | |
| <5 years | 61 (16.8) | 577 (18.8) | 1.38 (0.98-1.96) | 0.069 |
| 5-14 years | 80 (24.6) | 1046 (34.1) | 1.00 | |
| 15-18 years | 184 (56.6) | 1448 (47.2) | 1.66 (1.26-2.19) | <0.001 |
| [a]Gender | | | | |
| Male | 203 (62.5) | 1690 (55.0) | 1.36 (1.07-1.72) | 0.011 |
| Female | 122 (37.5) | 1381 (45.0) | 1.00 | |
| [a,c]Born in The Netherlands | | | | |
| Yes | 98 (30.2) | 1252 (40.8) | 1.00 | |
| No | 222 (68.3) | 1795 (58.5) | 1.58 (1.23-2.03) | <0.001 |
| Unknown | 5 (1.5) | 24 (0.8) | 2.66 (0.99-7.13) | 0.051 |
| [a,c]WHO Region of birth | | | | |
| European | 118 (36.3) | 1362 (44.4) | 1.00 | |
| African | 62 (19.1) | 565 (18.4) | 1.27 (0.92-1.75) | 0.151 |
| Eastern Mediterranean | 117 (36.0) | 879 (28.6) | 1.54 (1.17-2.01) | 0.002 |
| Americas | 1 (0.3) | 56 (1.8) | 0.21 (0.03-1.50) | 0.119 |
| South-East Asian | 6 (1.8) | 79 (2.6) | 0.88 (0.37-2.05) | 0.762 |
| Western Pacific | 16 (4.9) | 105 (3.4) | 1.76 (1.01-3.07) | 0.048 |
| Unknown | 5 (1.5) | 25 (0.8) | 2.31 (0.87-6.14) | 0.094 |
| [a]Immigrants or asylum seekers | | | | |
| No | 98 (30.2) | 1261 (41.1) | 1.00 | |
| Yes, duration <2.5 y | 134 (41.2) | 1139 (37.1) | 1.51 (1.15-1.99) | 0.003 |
| Yes, illegal immigrants | 17 (5.2) | 22 (0.7) | 9.94 (5.11-19.34) | <0.001 |
| Yes, duration >2.5 y | 37 (11.4) | 502 (16.3) | 0.95 (0.64-1.40) | 0.791 |
| Yes, duration unknown | 39 (12.0) | 147 (4.8) | 3.41 (2.27-5.14) | <0.001 |
| Area of living | | | | |
| Urban | 85 (26.2) | 854 (27.8) | 0.92 (0.71-1.19) | 0.526 |
| Suburban | 240 (73.8) | 2217 (72.2) | 1.00 | |
| TB notification and clinical characteristics | | | | |
| [a]Type of case finding | | | | |
| Passive | 170 (52.3) | 1478 (48.1) | 1.00 | |
| Active | 136 (41.8) | 1511 (49.2) | 0.78 (0.62-0.99) | 0.042 |
| Unknown | 19 (5.8) | 82 (2.7) | 2.01 (1.19-3.40) | 0.009 |
| [a]Known TB contacts | | | | |
| No | 274 (84.3) | 2090 (68.1) | 2.52 (1.85-3.43) | <0.001 |
| Yes | 51 (15.7) | 981 (31.9) | 1.00 | |
| Travelling in TB endemic area >3 months | | | | |
| No | 321 (98.8) | 3044 (99.1) | 1.00 | |
| Yes | 4 (1.2) | 27 (0.9) | 1.40 (0.49-4.04) | 0.528 |
| [a,d]Site of TB disease | | | | |
| PTB | 163 (50.2) | 1291 (42.0) | 1.00 | |
| EPTB | 118 (36.3) | 1452 (47.3) | 0.64 (0.50-0.82) | 0.001 |
| PTB + EPTB | 44 (13.5) | 328 (10.7) | 1.06 (0.74-1.51) | 0.737 |
| [a,d]Main localisation of TB | | | | |
| Primary TB infection | 30 (9.2) | 673 (21.9) | 0.54 (0.36-0.82) | 0.004 |
| Lungs | 107 (32.9) | 1302 (42.4) | 1.00 | |

| | | | | |
|---|---|---|---|---|
| Respiratory tract | 18 (5.5) | 388 (12.6) | 0.56 (0.34-0.94) | 0.029 |
| CNS | 7 (2.2) | 49 (1.6) | 1.74 (0.77-3.93) | 0.184 |
| Abdominal | 6 (1.8) | 51 (1.7) | 1.43 (0.60-3.41) | 0.418 |
| Osteoarticular | 6 (1.8) | 67 (2.2) | 1.09 (0.46-2.57) | 0.844 |
| Other organs | 33 (10.2) | 377 (12.3) | 1.06 (0.71-1.60) | 0.761 |
| Miliary | 9 (2.8) | 35 (1.1) | 3.13 (1.46-6.68) | 0.003 |
| Unknown | 109 (33.5) | 129 (4.2) | 10.28 (7.45-14.19) | <0.001 |
| Cavitary TB | | | | |
| No | 197 (60.6) | 2711 (88.3) | 1.00 | |
| Yes | 19 (5.8) | 231 (7.5) | 1.13 (0.69-1.85) | 0.620 |
| Unknown | 109 (33.5) | 129 (4.2) | 11.63 (8.67-15.59) | <0.001 |
| BCG-vaccinated | | | | |
| Yes | 117 (36.0) | 1163 (37.9) | 1.00 | |
| No | 107 (32.9) | 1167 (38.0) | 0.91 (0.69-1.20) | 0.508 |
| Unknown | 101 (31.1) | 741 (24.1) | 1.35 (1.02-1.80) | 0.035 |
| Had TB symptoms | | | | |
| No | 93 (28.6) | 930 (30.3) | 1.00 | |
| Yes | 199 (61.2) | 1688 (55.0) | 1.18 (0.91-1.53) | 0.213 |
| Unknown | 33 (10.2) | 453 (14.8) | 0.73 (0.48-1.10) | 0.132 |
| Patient's delay | | | | |
| No | 88 (27.1) | 781 (25.4) | 1.00 | |
| Yes, 1-4 weeks | 54 (16.6) | 608 (19.8) | 0.79 (0.55-1.12) | 0.189 |
| Yes, 5-8 weeks | 24 (7.4) | 168 (5.5) | 1.27 (0.78-2.05) | 0.334 |
| Yes, >8 weeks | 24 (7.4) | 225 (7.3) | 0.95 (0.59-1.52) | 0.821 |
| Unknown | 135 (41.5) | 1289 (42.0) | 0.93 (0.70-1.23) | 0.612 |
| Doctor's delay | | | | |
| No | 56 (17.2) | 577 (18.8) | 1.00 | |
| Yes, 1-4 weeks | 72 (22.2) | 556 (18.1) | 1.33 (0.92-1.93) | 0.125 |
| Yes, 5-8 weeks | 19 (5.8) | 137 (4.5) | 1.43 (0.82-2.48) | 0.206 |
| Yes, >8 weeks | 21 (6.5) | 237 (7.7) | 0.91 (0.54-1.54) | 0.733 |
| Unknown | 157 (48.3) | 1564 (50.9) | 1.03 (0.75-1.42) | 0.836 |
| Total delay (doctor + patient) | | | | |
| No | 9 (2.8) | 103 (3.4) | 1.00 | |
| Yes, 1-4 weeks | 40 (12.3) | 332 (10.8) | 1.38 (0.65-2.94) | 0.405 |
| Yes, 5-8 weeks | 20 (6.2) | 206 (6.7) | 1.11 (0.49-2.53) | 0.802 |
| Yes, >8 weeks | 49 (15.1) | 414 (13.5) | 1.35 (0.64-2.85) | 0.423 |
| Unknown | 207 (63.7) | 2016 (65.6) | 1.17 (0.59-2.36) | 0.650 |
| [a]Comorbidity | | | | |
| No/unknown | 314 (96.6) | 3031 (98.7) | 1.00 | |
| HIV positive | 7 (2.2) | 32 (1.0) | 2.11 (0.92-4.82) | 0.076 |
| Malignancy[µ] | 3 (0.9) | 4 (0.1) | 7.24 (1.61-32.49) | 0.010 |
| Others | 1 (0.3) | 4 (0.1) | 2.41 (0.27-21.66) | 0.431 |
| Bacteriological characteristics | | | | |
| Sputum smear microscopy | | | | |
| Negative | 58 (17.8) | 480 (15.6) | 1.00 | |
| Positive | 46 (14.2) | 433 (14.1) | 0.88 (0.58-1.32) | 0.536 |
| Unknown/ not done | 221 (68.0) | 2158 (70.3) | 0.85 (0.62-1.15) | 0.289 |
| BAL smear microscopy | | | | |
| Negative | 16 (4.9) | 109 (3.5) | 1.00 | |
| Positive | 15 (4.6) | 104 (3.4) | 0.98 (0.46-2.09) | 0.964 |
| Unknown/ not done | 294 (90.5) | 2858 (93.1) | 0.70 (0.41-1.20) | 0.195 |
| [a,e]Mycobacterial culture | | | | |
| Negative | 21 (6.5) | 319 (10.4) | 1.00 | |
| Positive | 187 (57.5) | 1734 (56.5) | 1.64 (1.03-2.61) | 0.038 |
| Unknown/ not done | 117 (36.0) | 1018 (33.1) | 1.75 (1.08-2.82) | 0.023 |
| [a,e]Species of Mycobacterium | | | | |
| *M. tuberculosis* | 151 (46.5) | 1372 (44.7) | 1.00 | |
| *M. bovis* | 5 (1.5) | 18 (0.6) | 2.52 (0.92-6.89) | 0.071 |
| Other *M. tuberculosis* complex | 3 (0.9) | 61 (2.0) | 0.45 (0.14-1.44) | 0.178 |
| Unknown | 166 (51.1) | 1620 (52.8) | 0.93 (0.74-1.17) | 0.546 |

| | | | | |
|---|---|---|---|---|
| [a]Drug susceptibility | | | | |
| Confirmed DS-TB | 39 (12.0) | 552 (18.0) | 1.00 | |
| Presumed DS-TB | 260 (80.0) | 2365 (77.0) | 1.56 (1.10-2.21) | 0.013 |
| Confirmed DR-TB | 26 (8.0) | 154 (5.0) | 2.39 (1.41-4.05) | 0.001 |
| Treatment characteristics | | | | |
| [a]Previously treated for TB | | | | |
| No | 273 (84.0) | 2796 (91.0) | 1.00 | |
| Yes | 13 (4.0) | 60 (2.0) | 2.22 (1.20-4.09) | 0.011 |
| Unknown | 39 (12.0) | 215 (7.0) | 1.86 (1.29-2.67) | 0.001 |
| Previously treated for LTBI | | | | |
| No | 54 (16.6) | 970 (31.6) | 1.00 | |
| Yes | 4 (1.2) | 78 (2.5) | 0.92 (0.32-2.61) | 0.877 |
| Unknown | 267 (82.2) | 2023 (65.9) | 2.37 (1.75-3.21) | <0.001 |
| [a]Drug dosing schedule | | | | |
| Daily | 56 (17.2) | 1085 (35.3) | 1.00 | |
| Intermittent[μ] | 3 (0.9) | 7 (0.2) | 8.30 (2.09-32.97) | 0.003 |
| Unknown | 266 (81.8) | 1979 (64.4) | 2.60 (1.93-3.51) | <0.001 |
| [a,†]Presence of ADR | | | | |
| No/unknown | 291 (89.5) | 2900 (94.4) | 1.00 | |
| Yes, single ADR | 20 (6.2) | 147 (4.8) | 1.36 (0.84-2.20) | 0.216 |
| Yes, multiple ADRs | 14 (4.3) | 24 (0.8) | 5.81 (2.97-11.36) | <0.001 |
| [a,†]Type of ADR | | | | |
| No/unknown | 291 (89.5) | 2900 (94.4) | 1.00 | |
| DILI | 9 (2.8) | 54 (1.8) | 1.66 (0.81-3.40) | 0.165 |
| Others | 25 (7.7) | 117 (3.8) | 2.13 (1.36-3.33) | 0.001 |
| [a]Treatment interruption >14 days | | | | |
| No | 42 (12.9) | 1045 (34.0) | 1.00 | |
| Yes | 11 (3.4) | 42 (1.4) | 6.52 (3.13-13.55) | <0.001 |
| Unknown | 272 (83.7) | 1984 (64.6) | 3.41 (2.44-4.76) | <0.001 |
| [a]Hospitalised ≥1 week | | | | |
| No/ <1 week | 238 (73.2) | 2153 (70.1) | 1.00 | |
| Yes | 68 (20.9) | 815 (26.5) | 0.75 (0.57-1.00) | 0.050 |
| Unknown | 19 (5.8) | 103 (3.4) | 1.67 (1.01-2.77) | 0.048 |
| [a]Supervised by PHNs | | | | |
| No | 32 (9.8) | 34 (1.1) | 1.00 | |
| Yes | 192 (59.1) | 2976 (96.9) | 0.07 (0.04-0.11) | <0.001 |
| Unknown | 101 (31.1) | 61 (2.0) | 1.76 (0.99-3.14) | 0.055 |
| [a]DOT | | | | |
| Yes | 50 (15.4) | 827 (26.9) | 1.00 | |
| No | 271 (83.4) | 2240 (72.9) | 2.00 (1.46-2.73) | <0.001 |
| Unknown | 4 (1.2) | 4 (0.1) | 16.54 (4.02-68.09) | <0.001 |

Data are presented as number (n) with percentages, unless stated otherwise: [#]median with interquartile ranges (IQR).

Abbreviations: ADR, adverse drug reactions; BAL, bronchoalveolar lavage; BCG, Bacillus Calmette Guerin; CI, confidence interval; CNS, central nervous system; DILI, drug-induced liver injury; DOT, directly observed therapy; DS-TB, drug-susceptible tuberculosis; DR-TB, drug-resistant tuberculosis; E, ethambutol; EPTB, extra-pulmonary tuberculosis; H, isoniazid; HIV, human immunodeficiency virus; LTBI, latent tuberculosis infection; OR, odds ratio; PHNs, public health nurses; PTB, pulmonary tuberculosis; R, rifampicin; Z, pyrazinamide.

[β]The sum of patients who achieved cure or completed treatment.

[¥]The sum of patients who died, were LTFU, or with unknown outcomes.

[a]Variable eligible for inclusion in multivariate analysis.

[b,c,d,e,f]Due to the likelihood of collinearity, only one of each of these variables was included during the development of the final multivariate model.

[μ]Excluded from multivariate analysis due to the low number of patients (<20).

**References for supplementary files:**


1. Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (NVALT). *Richtlijn Medicamenteuze Behandeling van Tuberculose*.; 2014. https://www.kncvtbc.org/uploaded/2015/09/3.4_tuberculose.pdf.
2. National Institute for Public Health and the Environment (RIVM). Osiris-NTR ziekte vragenlijst 2017. https://www.rivm.nl/documenten/osiris-ntr-ziekte-vragenlijst-2017. Published 2017.